C. elegans Neuroethology

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Synonyms

Nematode; Worm; Genetic control of behavior

Definition

In 1974, Sidney Brenner first introduced the nematode *Caenorhabditis elegans* as a model for studies of the genetic control of nervous systems and behavior [1]. Since then, a great deal of research has been focused on this 1 mm long roundworm. With its small nervous system, and fully sequenced genome, *C. elegans* is an excellent system in which to investigate the cellular mechanisms of behaviors such as foraging, feeding, defecation, movement, egg-laying, male mating behavior, sensory responses to touch, smell, taste and temperature, as well as simple forms of learning. It has a small and tractable nervous system, which consists of 302 neurons and approximately 5,000 chemical synapses [2]. Every neuron has been identified, its cell lineage traced and it connectivity patterns mapped [2]. Many of the *C. elegans* genes involved in coding its neural machinery are ►homologous to those in other organisms [3], including neurotransmitters, ►second messengers, ►growth factors and many metabolic pathways. Many different strategies are used to study neuroethology in *C. elegans*, including detailed behavioral analyses, laser ablation of identified neurons and mutants with alterations in genes expressed in specific neurons to determine the neural circuits underlying the behavior, genetic screens to determine genes involved in the behavior, modern genetic techniques to determine gene expression patterns and patterns of gene interaction. In this review, we will highlight several sensory behaviors, behavior plasticity and a foraging behavior as examples of how *C. elegans* can be used for studies of neural and genetic analyses of behavior.

Characteristics

Higher Level Processes: Modes of Sensory Input

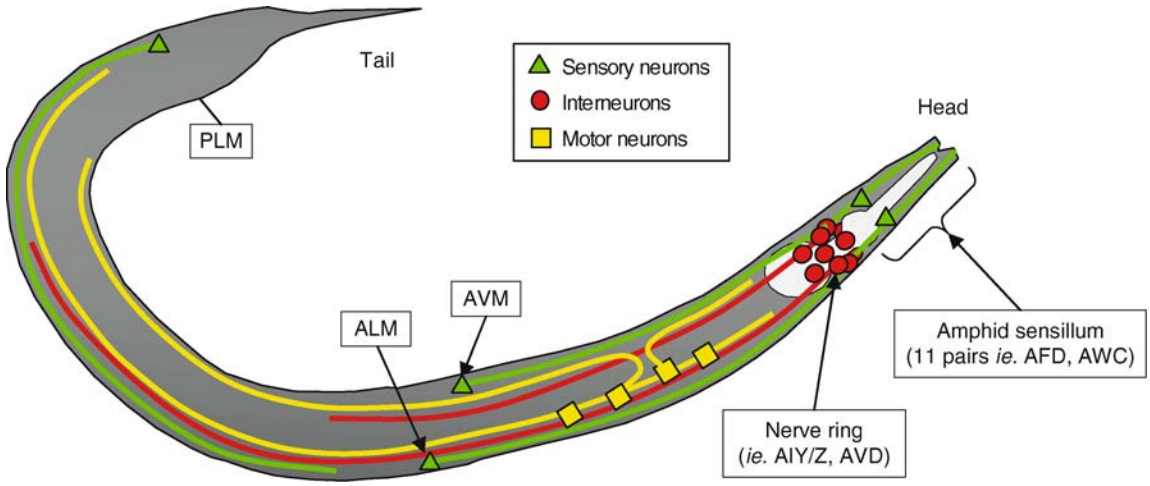
Studies of the behavior and anatomy of *C. elegans* have determined that *C. elegans* has three major types of sensory receptors: chemoreceptors, thermoreceptors and mechanosensory receptors [3]. *C. elegans* behavior and its ability to adapt to environmental cues are mediated by these three modes of sensory input, and allows for interesting investigations into the neural circuitry and genetic pathways that underlie these systems.

Lower Level Process: Chemotaxis

Studies investigating chemotactic behavior have used behavioral analysis, genetic manipulation and laser ablation (killing) of specific neurons to lead to the identification of the 22 specific chemosensory neurons necessary for *C. elegans* to detect and respond to different chemical cues [4]. The 11 pairs of chemosensory neurons located in the anterior amphid sensillum (nose; see Fig. 1) have been divided into two separate classes responsible for either the sensation of taste or smell.

Taste is defined as the detection of soluble compounds and is mediated by eight pairs of neurons (ADF, ADL, ASE, ASG, ASH, ASI, ASJ, ASK), while smell is defined as the detection of volatile compounds and is mediated by a separate set of three pairs of neurons (AWA, AWB, AWC) [4]. Despite its seemingly simple neural circuitry, *C. elegans* has the ability to discriminate between and respond to different chemical stimuli based on its previous experiences [5]. In essence, *C. elegans* can learn and form memories from chemosensory data.

Through the use of chemotaxis assays, hundreds of aqueous and volatile chemicals have been identified as either attractants or repellants to *C. elegans*. This ability to discriminate between attractants and repellents is essential in order for *C. elegans* to successfully navigate its soil habitat in terms of both feeding behavior and spatial orientation [6]. Further genetic investigations into the behavior of *C. elegans* have lead to the discovery of a group of 14 ►G-Protein Coupled Receptor subunits that are specifically involved in mediating chemotactic behavior [5,6]. Future comparisons of the physical structure and biochemical action



C. elegans Neuroethology. Figure 1 Drawing of *C. elegans* showing some of the elements of the neural circuitry involved in chemotactic, thermotactic, and mechanosensory behaviors; sensory neurons represented by triangles; interneurons represented by circles; motor neurons represented by squares. The neurons shown are representative of the neurons used for these behaviors, not all neurons in the circuits described in the text are drawn.

of these G-protein subunits and other signaling components will help to provide an even more detailed description of the chemosensory system and chemotactic behaviors of *C. elegans*.

A worm that is exposed to a taste or an odor for a long period of time decreases its response to the compound; this reversible decrease in response is called ►adaptation [5,6]. In *C. elegans*, olfactory adaptation to different volatile compounds is mediated by either AWA or AWC sensory neurons. When a worm is adapted to a particular odorant, the responses to other odors detected by the same sensory neuron are not affected indicating that adaptation is not a cell wide phenomenon, but rather is odorant specific. Mutations in two genes, *adp-1* and *osm-,9* expressed in the AWC sensory neurons, show normal initial responses to specific odors, however they fail to adapt to these odors [5,6]. This suggests that detection of odors and adaptation to the odors are separate processes. The expression of adaptation differs depending on whether worms are in the presence of food or not. Thus, olfactory adaptation is another complex form of ►behavioral plasticity that can be studied in this simple system.

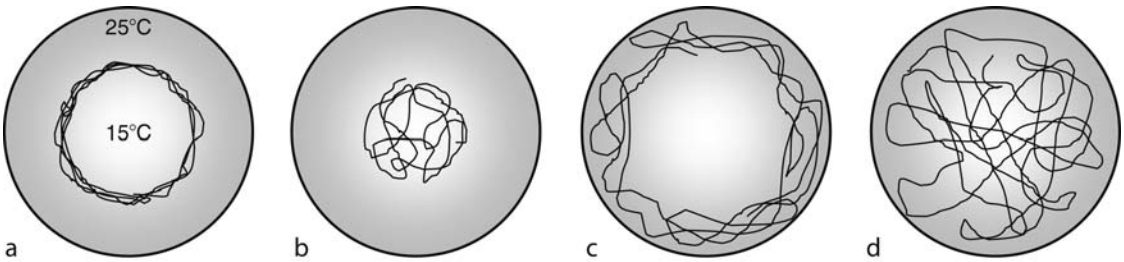
Lower Level Process: Thermotaxis

As early as 1975, *C. elegans* was observed to show a behavioral response to thermal gradients [7]. When *C. elegans* are cultivated in a well-fed state at a given temperature and then transferred to an environment containing a thermal gradient they will migrate to ►isotherms equivalent to the temperature in which they were raised (Fig. 2).

In contrast, worms experiencing starvation at a given temperature will avoid that temperature. This behavior appears to be the result of associative learning, where the worm learns to associate a specific temperature with the presence or absence of food.

In order for *C. elegans* to perform thermotaxis, they must be able to sense temperature. Laser ablation of any of the AFD, AIY, AIZ, and RIA neurons leads to animals with disrupted thermotactic behavior [5]. It is believed that the actual sensation of temperature is accomplished by AFD sensory neurons, whose specialized ►microvillus-like nerve endings are embedded just within the cuticle of the amphid sensillum in the nose of the worm [5]. The axon projects from the amphid towards the AIY, AIZ, and RIA interneurons in the nerve ring in the neck area of the worm [2]. Ablation of AIY or AIZ causes different abnormal behaviors, with *C. elegans* becoming either ►cryophilic or ►thermophilic, respectively, while killing RIA leaves worms unable to track temperatures (athermotactic). Mori and colleagues [5] have suggested that AIY and AIZ are interneurons integrated via direct synapses with the downstream interneuron RIA in order to produce the observed thermotactic response. When AFD neurons are destroyed using laser ablation, most but not all thermotactic behavior is arrested, indicating that there may be other neurons that have the ability to sense temperature; however, it is believed that most thermal information is collected by AFD [5].

Studies of mutants showing abnormal thermotactic behavior lead to the discovery of components that may be involved in the cellular mechanisms of thermotaxis. *tax-2* and *tax-4* are two genes that encode



C. elegans Neuroethology. Figure 2 Path of a *C. elegans* on an agar filled Petri dish with a radial thermal gradient of 15–25˚C after being well fed at 20˚C. Wild-type (N2) strain shows thermotactic behavior (a) Mutant strains, or laser-ablated wild-types can be abnormal showing cryophilic (b) thermophilic (c) or athermotactic behavior (d).

subunits of a ►cyclic nucleotide-gated cation channel. Mutants with disruptions of either *tax-2* or *tax-4* are athermotactic, completely ignoring thermal gradients [5]. When the gene products of *tax-2* and *tax-4* are tagged with ►green fluorescent protein, they are found localized to the membranes of the microvillus-like projections of AFD, suggesting an early role in the thermosensation mechanism [5]. Interestingly, the hypothesized TAX-2/TAX-4 channel is most similar to the cGMP-gated channels found in rod photoreceptors of the human retina that are important for visual sensation [5].

Thermotactic behavior in *C. elegans* has become model of learning and memory because worms are able to learn and remember a specific temperature and pair this memory with the appropriate feeding-state [5]. This memory can be modified simply by further cultivation for 2–4 h at a new temperature [7]. Recently, mutants have been discovered that can memorize a cultivation temperature but cannot couple it to a feeding state [5], suggesting that these processes are two distinct mechanisms.

Lower Level Process: Mechanosensory Behavior

C. elegans responds to mechanosensory stimuli, in response to a touch to the head worms will swim backwards, in response to a touch to the tail worms will swim forwards. In addition, worms will swim backwards in response to a mechanical tap to their surroundings, such as within a laboratory Petri dish [8]. This tap-withdrawal response is a perfect example of how a seemingly simple behavior has more complexity than it originally appears; this response is plastic and shows short-term ►habituation and dishabituation, ►context conditioning and long-term memory for habituation [8]. Short-term habituation occurs with a series of taps separated by an inter-stimulus interval (ISI). Short ISIs lead to fast decreases in the withdrawal response, but this response is recovered quickly. Worms exposed to long ISIs, on the other hand, take longer to fully habituate, but have a much longer recovery period [8]. The tap-withdrawal response can also show long-term memory of habituation lasting at least 24 h [8]. The neural circuit for the tap response consists of the mechanosensory neurons ALM, AVM and PLM and the interneurons AVA, AVB, AVD and PVC [8]. Behavioral experiments led to the hypothesis that plasticity was occurring at the synapse between the sensory neurons and interneurons [8]. This synapse uses glutamate as its neurotransmitter, thus mutations that affect glutamate transmission affect both short-term and long-term memory. Mutations in the gene *eat-4,* which is responsible for expressing a pre-synaptic vesicular glutamate transporter, causes more rapid and complete short-term habituation of the tap-withdrawal response and no dishabituation [8]. When *C. elegans* have mutations in the gene, (*glr-1*) a post-synaptic glutamate receptor, no long-term memory of habituation is observed [9]. This indicates that glutamate transmission between mechanosensory neurons and interneurons is necessary for short-term and long-term memory for habituation of the tap-withdrawal response in *C. elegans*. This is of special interest because glutamate transmission has been implicated in long-term memory in many different animals [9], and may be part of a primitive, highly conserved mechanism of memory.

Higher Level Process: Natural Variation in Feeding Behavior

Natural variations in feeding behavior have been identified within *C. elegans* populations [10]. Wild type (N2) strains feed in a solitary fashion, they slow down when they contact food, and disperse randomly as they feed. *C. elegans* variants such as the RC301 strain and *npr-1* mutants show a feeding pattern whereby they forage for food in groups, they speed up when they contact food and they congregate at the edges of food patches where levels of oxygen are low [10]. The differences between the solitary and social strains are the result of a single amino acid substitution in the gene *npr*-1 (a predicted G protein-coupled receptor of the neuropeptide Y receptor family). The *npr-1* gene is expressed in several neurons (AQR, PQR and URX) that are exposed to *C. elegans* body fluid, and are involved in

monitoring oxygen levels [10]. This research demonstrates how a "social" behavior can be dissected genetically, allowing a deeper understanding of the ways that neurons can produce and regulate behavior.

Summary

Detailed behavioral studies of the worm have shown that this tiny creature has a rich and complex behavioral repertoire, making it an ideal system in which to unravel the mysteries of the cellular control of behavior. Findings such as those described here contribute to the ever-growing database of knowledge within the *C. elegans* community. This database of knowledge (much of it available via the internet), coupled with the development of new investigative techniques, allows for research to be conducted at the behavioral, neuronal and genetic level making *C. elegans* an ideal model for the study of how genes regulate behavior.

Each of the examples that we have described show some of the ways that having all of the neurons in the nervous system identified and knowing their connectivity, as well as having a fully mapped and sequenced genome, has greatly aided the investigations of the roles of identified genes in behavior and extended our understanding of the neuroethology of *C. elegans*.

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C Fiber

Definition

The C fiber is an unmyelinated axon (less than 1 μm in diameter) found in a peripheral nerve trunk. It conducts pain and temperature senses.

►Development of Nociception

C1 - C2 Cell Groups (Adrenergic Cell Groups)

Definition

The C1-C2 (and C3) cell groups are adrenergic cells groups located in the medulla. They contain the enzyme that converts norepinephrine to epinephrine. Projections to several regions have been found: paraventricular nucleus of the hypothalamus; locus coeruleus; solitary nucleus; dorsal motor nucleus of the vagus; and intermediolateral cell column of the spinal cord.

Ca^{2+}

Definition

The divalent calcium ion. Calcium is a light metal with atomic number 20, atomic mass 40.08, ionic radius 94 pm, and hydrated Ionic radius 410 pm.

Ca^{2+} Channels

Definition

►Calcium Channels – an Overview

Ca^{2+}-activated Cl^- Channels

Definition

►Chloride Channels and Transporters

Ca^{2+}-dependent K^+ Channels (KCa)

Definition

A type of voltage-gated ion channel specific for K^+ ions, which requires the binding of Ca^{2+} ions to its internal surface to be gated open. Ca^{2+} is an important intracellular signaling molecule in neurons.

►Neuronal Potassium Channels

Ca^{2+} Microdomain

Definition

A localized increase in the cytosolic free Ca^{2+} concentration in the vicinity of open Ca^{2+} channels at the plasma membrane (e.g. the active zone; more likely to be on the scale of tens of nanometers) or intracellular Ca^{2+} stores (e.g. store-operated Ca^{2+} channels; generally referred to as Ca^{2+}-induced Ca^{2+} release). These microdomains generally serve triggering/signaling roles.

►Synaptic Proteins and Regulated Exocytosis

CA1

Definition

A part of brain regions in the hippocampus, which receives synaptic inputs mainly from the hippocampal CA3 region through Schaffer collaterals. The output from CA1 pyramidal cells is sent to the cerebral cortex.

►Associative Long-Term Potentiation (LTP)
►Long-Term Potentiation (LTP)
►Memory, Molecular Mechanisms

CA3

Definition

A part of brain regions in the hippocampus, which receives synaptic inputs from the dentate gyrus and the CA3 pyramidal cells of the ipsilateral and contralateral hippocampi. The output from CA3 pyramidal cells is sent to the CA1 region via Schaffer collaterals and to the CA3 region via associational/commissural fibers.

►Associative Long-Term Potentiation (LTP)
►Long-Term Potentiation (LTP)
►Memory, Molecular Mechanisms

Cable Theory

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Definition

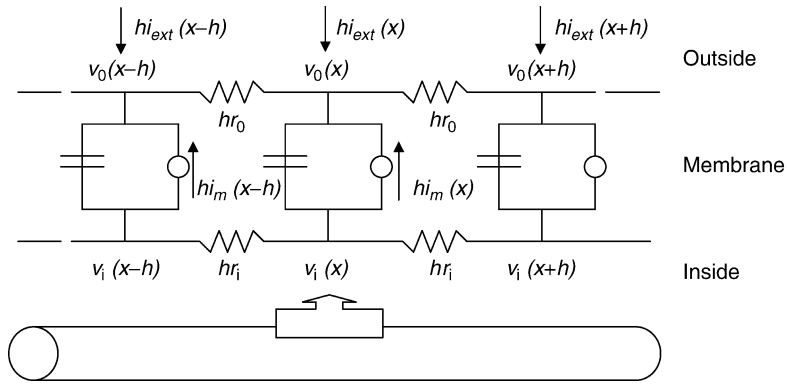
Voltage signals in neurons travel down thin, long, cable-like dendritic and axonal processes. The theoretical modeling and mathematical/computational analysis of signal propagation within these processes is called cable theory. Due to the initial important work of Rall (see [1] and references therein), much of the focus has been concerned with the effects of ►synaptic inputs propagating to the cell's soma, how these inputs interact with each other, and how inputs to various dendritic tree locations affect the neuron's output signal.

Characteristics

Modeling various observed neural properties, where variations of voltage with location are important, leads to a partial differential equation description of the evolution of electrical potential in the neuron. For understanding information processing in neural networks, the contributions of individual neurons and their dendritic trees takes on central importance.

In the ►core conductor model of a neural process, cable theory classically has assumed a cylindrical membrane with an electrically conducting core. The core cross-section is sufficiently small compared to the length of the fiber that the core can be considered as cross-sectionally isopotential. Thus, the cable model only depends on voltage differences in the axial direction. The cell membrane is surrounded by extracellular space that is assumed isopotential. These considerations conveniently allow visualization of a circuit model for the membrane (see Fig. 1) from which the mathematical model is derived via ►Kirchhoff's conservation laws.

One can also start from the more fundamental ►Maxwell's equations. Some other assumptions behind the model include the neuron's electrical membrane properties being uniform (constant), and the intracellular and extracellular spaces having homogeneous electrical properties. Also, magnetic field effects



Cable Theory. Figure 1 A representation of a segment of dendritic cylinder cable and a discrete electrical circuit model of a dendritic membrane segment. Intracellular and extracellular longitudinal currents and resistances per unit length of cable are, respectively, $i_i(x)$,$i_0(x)$,r_i,r_0; $v_i(x)$,$v_0(x)$ are the intracellular and extracellular potentials, at x. Also indicated is the external current per unit length of cable, i_{ext}(x), and $i_m(x)$ is the sum of ionic currents and current through the membrane ►capacitance, per unit length of cable, at x. For convenience the time dependence of the potentials and currents has been notationally suppressed.

are negligible and the membrane can be modeled by a ►capacitor in parallel with a ►conductance. The steps to deriving the cable equation from the circuit model in Fig. 1 involve writing current conservation equations for each node, using ►Ohm's law between nodes, and taking appropriate limits as the spacing between nodes goes to zero in order to arrive at the differential equation model. With the definition that the trans ►membrane potential is the difference between the intracellular and the extracellular longitudinal potentials, that is $v = v_i - v_0$, (notation from Fig. 1), then after some algebra the cable equation becomes

$$c_m \frac{\partial v}{\partial t} + i_{ion} = \frac{1}{r_0 + r_i} \frac{\partial^2 v}{\partial x^2} + i_{ext} \qquad (1)$$

This is really just a statement that the total membrane current (right side of equation), including external source current i_{ext}, is just the sum of ►capacitance and resistive (ionic) currents. Details of the derivation can be found in various references; see, e.g. [2]. The source current i_{ext} can be a sum of point synaptic currents, or an externally applied current stimulus. The extracellular and intracellular longitudinal resistances per unit length of cable are r_0, r_i, respectively, and r_0 is usually so much smaller than r_i that it is ignored ($r_0 = 0$). Representative values of some of the parameters are given in Table 1.

Some Special Problems for Passive Cables

If the membrane is passive (no active ion channels), the membrane element represented by the circles in Fig. 1 become resistor-battery elements. Using E as a constant ►rest(ing) potential for the cell, and $g_m = 1/r_m$ as a constant membrane conductance, then $i_{ion} = g_m \times (v - E)$. Also, a scaling more compatible with measurements, and using a = cylinder's (uniform) radius, define $R_i = r_i \pi a^2$, $R_m = r_m/2\pi a$, and $C_m = c_m/2\pi a$. Ignoring external current sources ($i_{ext} = 0$), and substituting these into (1), one arrives at the linear cable theory model

$$C_m \frac{\partial v}{\partial t} + \frac{v - E}{R_m} = \frac{a}{2R_i} \frac{\partial^2 v}{\partial x^2}. \qquad (2)$$

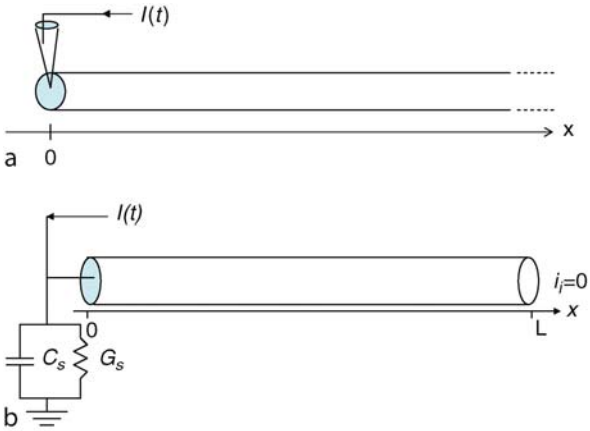
The cable's ►space constant is given by $\lambda = \sqrt{r_m/r_i} = \sqrt{aR_m/2R_i}$. To illustrate the nature of λ, consider the time independent problem (that is, drop the t-derivative in (2)) of a very long cable that for all intents one can take as semi-infinite (defined for $x > 0$). Impose at $x = 0$ a constant current step stimulus, I_0 (see Fig. 2a).

The appropriate boundary condition is given by $\frac{dv}{dx}(0,t) = -I_0/G_\infty$. Here G_∞ is the input conductance, and is given by $G_\infty = 1/\lambda r_i = 1/\sqrt{r_m r_i} = \sqrt{2\pi^2/R_i R_m} a^{3/2}$. If we let $\tilde{v}(x)$be the deviation of potential away from the fiber's rest potential, that is, $\tilde{v}(x) = v(x) - E$, where $v(x)$ is the bounded, time independent solution to (2) for all $x > 0$, with this boundary condition at $x = 0$, then $\tilde{v}(x) = \tilde{v}(0)e^{-x/\lambda} = (\lambda I_0/G_\infty)e^{-x/\lambda}$. Thus, the ►depolarization decays exponentially, and $x = \lambda$ is the value where $\tilde{v}$ has dropped to $1/e$ times the initial value $\tilde{v}(0)$. Hence, the smaller λ is, the faster the decay, and the less the stimulus is felt down the fiber. Injection of a known constant current at the terminal, then measuring the steady-state voltage response will determine λ from the decay of potential. Since the cell's rest potential is measurable, knowledge of $v(0) - E = \lambda I_0/G_\infty$ gives G_∞, hence r_i. Since $\lambda = \sqrt{r_m/r_i}$, r_m can be determined. A couple of typical values of λ are given in Table 1. With the parameters determined the time dependent problem can be solved exactly and various questions can be explored (see [5]).

Cable Theory. Table 1 Representative parameter values (adapted from [3])

Symbol	Units	Squid giant axon	Cat spinal motoneuron
R_m	$\Omega - cm^2$	1000	2500
C_m	$\mu F/cm^2$	1	2
R_i	$\Omega - cm$	30	60
r_i	Ω/cm	15×10^3	8.9×10^7
a	μm	250	10 (primary dendrite)
τ	ms	1	5
λ	μm	6500	1000

A simple case to consider is Rall's ►motoneuron ([4]; see Fig. 2b). If the cable has physical length L (electrotonic length L/λ), then a reasonable boundary condition at $x = L$ is to have zero axial current. This is commonly the boundary condition used for the terminus of dendritic branches. With longitudinal current being proportional to the spatial derivative of potential, this ("sealed-end") boundary condition just states that this spatial derivative of v equals zero at $x = L$, for all time $t > 0$. In Rall's model the soma is a (passive) point soma representation with capacitance C_s and conductance G_s. Then the left-end (somatic) boundary condition is a linear combination of potential and its space and time rates of change at $x = 0$. This addition to the cable model became the basis for improvements in various parameter estimation formulas that could be correlated with experimental findings. See [1,4] for details.



Cable Theory. Figure 2 (a) A representation of a semi-infinite cylinder cable with a step applied current imposed at the left end ($x = 0$). (b) A representative drawing of Rall's motoneuron model [4], indicating his point-soma circuit with capacitance C_s and conductance G_s. Also indicated is an applied current injected at the soma. The cable is of finite length, with a sealed-end condition (no longitudinal current flow) at the right end.

Passive Dendritic Trees and Rall's Equivalent Cylinder Theorem

In the motoneuron model above the dendritic structure is represented by a single cylinder. Under certain constraints a branching structure can be reduced to a single ►electrically equivalent cylinder model [2,3]. This approach has proved quite useful in interpreting various experimental observations [1]. The structure Rall set up is flexible enough to handle arbitrary branching geometries where the branches may have nonuniform membrane properties.

To give some idea of the assumptions needed (consult [2] for details) consider first a simple tree with a "trunk" segment connected to a soma (at $x = 0$), and at each branch point of the tree there is a parent branch (with radius a_{parent} in the direction of the soma, and some number of sibling branches emanating from it. Some assumptions imposed on the tree are: the initial depolarization is the same at all points equal distance from the soma (for instance, the whole tree is at its rest potential), and each dendritic tip has the same terminal boundary condition (e.g., the sealed-end condition). Also, at each branching point a three-halves law is assumed to hold: $(a_{parent})^{3/2} = \sum_i a_i^{3/2}$, the sum taken over all sibling branches i associated with the specific parent branch. This can be considered an ►impedance matching condition, and it is a reasonable physiological approximation in many cases [3]. Rall had the assumption that with distances measured in space constants λ, the dendritic terminal points were assumed to be at the same electrotonic distance from the soma. This is generally not satisfied; dendritic tips can vary considerably across branches. This may have the effect that an ►equivalent cylinder actually tapers gradually to zero moving from the soma to its terminus. However, the assumption has been weakened in later generalizations of the theory. With these conditions the depolarization at any point in the tree can be determined from the solution to the cable equation at the same distance from the soma.

There are relatively few problems of interest that can be solved analytically and so one must resort to

numerical methods. Because of morphological complexity of dendritic trees and the need to investigate the effects of distributed synaptic inputs, there are now excellent modeling simulation tools available that take the philosophy that cables and trees can be segmented into numerous compartments.

Nonlinear Cable Theory

If the ►membrane potential is not relatively close to the neuron's rest potential, and the cable has active ion channels, then the ►current-voltage relation i_{ion} in (1) has nonlinear dependence on voltage. The most important and most studied example of this is the ►Hodgkin–Huxley model [6]. The Hodgkin-Huxley model for ►squid giant axon could reproduce and explain a large range of data, including shape and ►conduction velocity of a propagating action potential (impulse), its sharp threshold, ►refractory period, anode-break excitation, ►accommodation, and subthreshold oscillations. The conductance-based modeling framework formulated by the Hodgkin-Huxley model has remained remarkably flexible for modeling other neural processes, including some human neuronal processes.

Much of the analysis of the cable model of Hodgkin and Huxley (including later modifications, generalizations, and simplifications) has concerned the initiation and behavior of single impulses and pulse trains under various circumstances. Examples include dependence of conduction speed on temperature, density of ►sodium channels, conductance properties, initiation and sustained firing patterns, etc. (see, e.g. [5]).

Dendrites (and axons) are very non-uniform, particularly in geometry and distribution of ionic channels. Generalizations of classical cable theory have tried to assess a functional role for these non-uniformities, taking into consideration the cell type, but results are rather scattered. The effect on conduction when there are present significant changes in dendritic cable diameter has had a long history. The main issues here concern conditions for conduction block (stopping spike propagation), and reflecting "echo" waves that back propagate [7]. This behavior may have functional consequences regarding synaptic activity. Also, the distribution of ►dendritic spines on a cable can determine whether signal propagation will be successful. Simulations show that sometimes clumping of spines is needed for successful conduction [8]. As an example of another study, model simulations of a cable show amplification of ►excitatory post-synaptic potentialseven when there are only persistent sodium channels that are sparsely distributed in isolated clumps [9].

Myelinated Cable Modeling

The most extreme non-uniform case is that of myelinated (myelination) axons. Because sodium channels are concentrated at ►nodes of Ranvier, and various ion channels are in relatively low density in the ►internodes, theoretical models have concentrated on saltatory aspects of conduction (salutatory conduction), and have incorporated spatially discrete dynamics. These models assumed the internodes were perfect insulators. Cable theory based models have considered the internodes as passive cable segments, separated by active nodes (see, e.g. [2]). Simulations have indicated that internodal structure and parameters have far more control on velocity than does the node, though the nodal characteristics are important for getting the correct threshold level. Analysis and simulation studies have most often been concerned with the dependence of conduction velocity on parameters such as diameter ratio between node and internode, internodal length, temperature, ratio of capacitances, etc. For example, if the internodal length and internodal diameter (with ►myelin sheath) is, respectively, L and D, and d is the axon diameter, then conduction velocity tends to be insensitive to d/D and L/D over a range of values, and tending to increase linearly with d, other parameters being fixed. Where investigated, conduction will proceed through one unexcitable node, but if there are two adjacent unexcitable nodes conduction block will generally occur. Some studies have looked at the effects of ►demyelination and partial remyelination on conduction characteristics. For example, Waxman and Brill [10] studied conduction near demyelinated regions. The reduction in length of two internodes closest to the demyelinated regions to approximately one third of their normal length or less will still facilitate conduction.

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CaCC

Definition
►Ca^{2+}-activated Cl^- Channels

►Chloride Channels and Transporters

Caecilians

Definition
A group of long bodied, limbless living amphibians.

►The Phylogeny and Evolution of Amniotes

Caenorhabditis

Definition
Worm of the phylum Nemathelminthes, class Nematodes. Nematodes are special, because they have constant cell numbers. Caenorhabditis has served as model system for genetics and development, but also for many different aspects of behavior (see essay on "Neuroethology of behavior in caenorhadbitis").

Calcarine Sulcus

Synonyms
Sulcus calcarinus; Calcarine sulcus

Definition
Typical groove running on the median side of the occipital lobe, often entering the parietooccipital sulcus.

Area 17, the striate cortex, stretches along this sulcus.

►Telencephalon

CADASIL

Definition
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukencephalopathy. Hereditary stroke disorder that is caused by mutations of the Notch 3 gene on chromosome 19.

►Ischemic Stroke
►Stroke

Cadherins

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Synonyms
Cadherin superfamily

Definition
Founding members of the cadherin superfamily were identified by their ability to mediate calcium-dependent cell-to-cell adhesion. They were designated as cadherins (*ca*lcium + *adher*e + prote*in*) and are now classified as classical cadherins. Classical cadherins are type I transmembrane proteins and defined by two additional structural features (Fig. 1). One is the extracellular cadherin repeat or cadherin domain of roughly 110 amino acids, which mediates calcium-dependent homotypic interaction between cells. This domain is typically organized in tandem repeats. Another is the intracellular domain with which a group of cytoplasmic molecules, i.e., ►catenins, interact. In addition to classical cadherins, the cadherin superfamily includes many subfamilies of non-classical cadherins [1,2]. Although non-classical molecules also have cadherin repeats in their ectodomains, they lack the catenin-binding motif and are characterized by a variety of transmembrane domains and intracellular sequences. Non-classical

cadherins include desmosomal cadherins, protocadherins and seven-pass transmembrane cadherins. "Cadherin" is used as a synonym for classical cadherin hereafter.

Characteristics

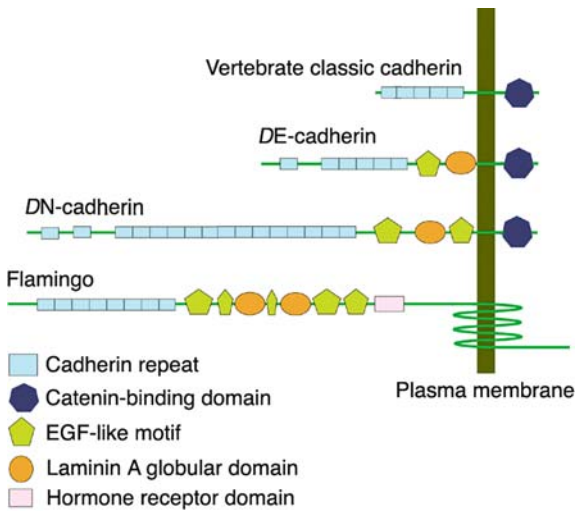
Quantitative Description

In a single vertebrate species such as humans, over 20 different subtypes of classical cadherins have been found so far, whereas the total number of non-classical cadherins is 80 at a moderate estimate.

Description of the Structures

Each vertebrate classical cadherin has five cadherin repeats, whereas the number of repeats and the presence or absence of other extracellular motifs are variable among invertebrate cadherins [1,2], even in a single species such as *Drosophila* (Fig. 1).

Compared to other cell-surface molecules, such as calcium-independent cell adhesion molecules, cadherins are unique in their ability to induce tight cell aggregates in which cells adhere to neighbors with maximum areas of contact. This ability appears to be dependent on the interaction of the cadherin–catenin multiprotein complex with the actin cytoskeleton. The classification of non-classical cadherins is based on sequence similarities of their intracellular regions and the overall structure of all domains. It is reasonable to assume that distinct subfamilies of non-classical cadherins are responsible for different functions and that they are coupled to different signaling pathways that have been under investigation.



Cadherins. Figure 1 Structural diversity of the cadherin superfamily. Overall structures of four selected members of the cadherin superfamily: a vertebrate classical cadherin (about 750 amino acids in length), two *Drosophila* classic cadherins (*D*E and *D*N are 1,507 and 3,108 respectively) and the *Drosophila* seven-pass transmembrane cadherin, Flamingo (3,575). Both vertebrate and *Drosophila* classical cadherins have catenin-binding domains, although the number of repeats and the presence or absence of other extracellular motifs are variable.

Higher Level Structures and Their Regulation

3D Structure of Ectodomains

In the presence of calcium, cells expressing a certain subtype of classical cadherins only form stable contacts with cells expressing the same type, with some exceptions. This homotypic adhesion between cells arises from homophilic interactions between ectodomains of the same subtype and consequently differential expression of cadherins underlies various roles in vivo (as explained later). Many different structural approaches have been used to unravel the molecular basis for cadherin-mediate adhesion. Although several different models of the cadherin homophilic bond have been proposed, all essentially agree that the specificity lies in the most N-terminal part of the ectodomains and that molecular interaction occurs not only between adjacent cells (in trans), but also on the surface of the same cell (in cis) [3]. A study using a two-repeat fragment of E-cadherin showed that calcium-binding in between consecutive repeats stabilizes otherwise flexible linker regions.

Distinct Protein Complexes at Two Intercellular Junctions

Classical cadherins, one subfamily of non-classical cadherins (desmosomal cadherins) and their associated proteins are structural components of intercellular junctions that were previously documented at the electron microscopic level. In polarized epithelial cells, the adherens junction (AJ) is formed near the apical surface and E-cadherin is typically localized there [2,4]. Catenins assemble on the intracellular domain of E-cadherin and this complex is linked to the cortical actin. An AJ is not necessarily a stable structure. Epithelial cells regulate their contacts with neighboring cells during development and in disease states such as tumor metastasis. Underlying mechanisms include endocytic recycling of cadherin and loss of one of the catenins by mutations respectively [5]. A synapse contains cadherins and catenins and is structurally similar to an AJ (see below).

A desmosome is another type of intercellular junction that is abundant in tissues that experience mechanical stress, where two subtypes of desmosomal cadherins, desmocollins and desmogleins, are localized. Heterodimers of desmocollin and desmoglein are linked to the keratin intermediate filament cytoskeleton via interactions with one of the catenins, plakoglobin, and other components of the desmosome.

Function

Cell Sorting, Cell Rearrangement and Epithelial to Mesenchymal Transitions

Maintenance of solid tissues is just one of the multiple missions of classical cadherins. Differential expression of cadherin subtypes and spatiotemporal control of cadherin–catenin activity play pivotal roles in dynamic morphogenetic events that take place numerous times during development [1,6,7]. Such tissue morphogenesis can be classified at least into three categories. First there are numerous examples demonstrating that cell populations expressing different cadherins sort out in vivo and boundaries are generated between them. For example, expression of N-cadherin in the presumptive neural epithelium allows it to separate from the E-cadherin-expressing ectoderm. Other examples are the roles of cadherins in the establishment/maintenance of early embryonic brain divisions. Second, dynamic breaking and reforming of cadherin adhesive cell–cell binding is required for cells to change neighbors and this cell rearrangement controls the reshaping of tissues. Third, epithelial cells are often converted to motile, fibroblast-like cells and a hallmark of this epithelial to mesenchymal transition is decreased expression of E-cadherin. Down-regulation or dysfunction of E-cadherin also plays a part in tumor cell invasion and metastasis.

Axonal and Dendritic Outgrowth, Fasciculation, Pathfinding and Target Recognition

A number of classical cadherins are distributed in axons during the period of active elongation and the expression of most vertebrate cadherins studied to date is restricted to subsets of growing fiber tracts. It therefore has been assumed that cadherins are used by growth cones to navigate along pre-existing pathways expressing the same type of cadherin. A number of in vitro experiments indicate that N-cadherin is an excellent substrate for axonal outgrowth from N-cadherin-positive neurons and is also required for axonal fasciculation. Furthermore in vivo analyses have strengthened or demonstrated roles of cadherins in various aspects of neuronal network formation including axonal and dendritic outgrowth, fasciculation, pathfinding and target recognition [2,7,8].

In the Xenopus visual system, expression of a dominant negative form or injection of antibodies against N-cadherin cause loss or reduction of neurite growth or pathfinding errors. Genetic studies in *Drosophila* and *C. elegans* have shown that loss of N-cadherin function causes defective axonal fasciculation and pathfinding errors in mutant animals. In the fly visual system, N-cadherin appears to mediate a homophilic, attractive interaction between photoreceptor growth cones and their targets that precedes synaptic partner choice. An important role of cadherin in dendrodendritic interaction is shown in the fly olfactory system. N-cadherin confines dendritic terminals of projection neurons (counterparts of vertebrate mitral cells) to a particular glomerulus following an initial overgrowth into adjacent glomeruli.

Non-classical cadherins also regulate neuronal wiring; for example a series of recent studies have revealed that seven-pass transmembrane cadherins are involved in regulation of dendritic growth. The *Drosophila* seven-pass transmembrane cadherin Flamingo (Fmi; also known as Starry night) is required for sensory neurons and central mushroom-body neurons to restrict dendritic growth. In contrast to the overextension phenotypes in the fly nervous system, knockdown of one of the mammalian Fmi homologs, Celsr2, by a RNA interference (RNAi) approach in pyramidal and Purkinje neurons reduced branch number and length, leading to simplification of dendritic arbors. What the downstream signal transduction pathways are and why loss of Fmi function and knocking down of Celsr2 produce superficially opposite phenotypes are under investigation. Another vertebrate homolog, Celsr3, is required for formation of major axonal fascicles in the mouse brain.

Synaptogenesis and Synaptic Plasticity

After axons traverse long distances and reach correct target regions, these axons and the dendritic filopodia of their target cells recognize each other and subsequently form a synapse. Neurons utilize the characteristics of classical cadherins to "zip synapses up." Classical cadherins are detected at the earliest points of axon-filopodial contact and persist in mature synapses where cadherins and catenins are localized in the close vicinity of the transmitter-release zone, although this varies according to the type of synapse. Roles of cadherins and catenins in synapse formation have been examined in cultured mammalian neurons and in the visual system of *Drosophila* mutants. These studies have indicated that the cadherin–catenin system is required for stabilizing contacts between incoming axons and targets, morphological maturation of synapse and the maintenance of stable synaptic contacts through regulating spine motility [2,7,8,9]. A sub-class of protocadherins, protocadherin γ, is also found in synaptic junctions.

Multiple subtypes of classical cadherins are expressed in the brain and their expression profiles often correlate with neuronal connectivity. This finding, together with the homophilic binding specificity of individual subtypes, led to the proposal that the differential binding among the subtypes may connect pre- and post-synaptic membranes and lock them together, thus forming selective neuronal connections. Many protocadherins are also expressed in the nervous system. Thus it is intriguing to envisage whether the molecular diversity of classic cadherins and protocadherins play a role

in specifying synaptic connectivity and if so, how the roles of these two different subfamilies came to be differentiated.

Cadherins are also important physiologically. Application of anti-N-cadherin antibodies to hippocampal slices indicated that N-cadherin is needed to hold nascent synaptic contacts and establish L-LTP. The functions of cadherins and catenins have been studied at the behavioral level as well. For example, LTP is elevated in hippocampal neurons in cadherin-11-knockout mice. This observation has been explained by assuming that reducing the activity of cadherin might enhance the deformability of spines, so rendering them more sensitive to LTP-inducing stimuli.

Planar Cell Polarity

In many organs, epithelial cells are polarized not only along the apicobasal axis, but also along a second axis within a plane. Acquisition of the latter polarity, known as planar cell polarity (PCP) or tissue polarity, is crucial for specialized cellular functions. A typical example of PCP is seen in the sensory epithelium of the inner ear, where stereocilia that protrude from the apical surfaces of hair cells are uniformly oriented. This coordinated alignment maximizes the ear's sensitivity to sound and acceleration. Genetic programming of PCP has been thoroughly studied in *Drosophila*. Such studies highlight the pivotal roles of three non-classic cadherins, the seven-pass transmembrane cadherin Flamingo (Fmi) and the single-pass transmembrane proteins Dachsous (Ds) and Fat (Ft) [1,2,10]. It was previously postulated that polarity information is passed from one end of a tissue to another, possibly via a secreted factor; nowadays it is speculated that direct cell–cell interaction, mediated by Ds–Ft heterophilic interaction, transmits polarity locally within the tissue and that subsequently Fmi is involved in polarization of individual cells. All of the three *Drosophila* molecules are conserved in vertebrates and at least one of the Flamingo homologs has been shown to be required for acquisition of PCP in the mouse inner ear.

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Cadmium-insensitive Pacemakers

Definition

Pacemaker neurons that are dependent on persistent sodium (Na^+) current and burst in the presence of cadmium.

►Persistent Na^+ Currents
►Respiratory Pacemakers

Cadmium-sensitive Pacemakers

Definition

Pacemaker neurons that depend on calcium-activated non-specific cation (CAN) current and are blocked by cadmium.

►Calcium-activated Non-specific Cation (CAN) Current
►Respiratory Pacemakers

Calcitonin Gene Related Peptide (CGRP)

Definition

CGRP is one of the numerous peptides found in neurons and acting as co-transmitters. It is derived from the gene

encoding calcitonin by alternative splicing of mRNA and by proteolytic processing of a precursor peptide. It is mainly found in sensory neurons of the central nervous system. Its prime target is the CGRP receptor, a member of the family of G protein-coupled receptors. In contrast to calcitonin, which is involved in calcium homeostasis and bone remodelling, CGRP causes vasodilatation and vascular leakage. It is expressed in group C sensory nerve fibers. It works as a stimulatory (pro-nociceptive) neurotransmitter when it is released centrally, and as a pro-inflammatory mediator when released peripherally. The central role of CGRP in primary headaches has led to a search for suitable antagonists of CGRP receptors.

Calcium-activated Non-specific Cation (CAN) Current

Definition

An inward current that is generated by ion channels that open in response to an increased intracellular calcium concentration. The opening of these ion channels leads to an inward current that is carried by non-specific cations including calcium and sodium ions. The CAN current has been implicated in generating pacemaker activity in various pacemaker neuron types.

►Bursting Pacemakers

Calcium Binding Proteins

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Synonyms

Syt; 65-kDa synaptic vesicle protein; CaMKII; Type II Ca/Calmodulin-dependent kinase

Definition

Syt: A putative major ►Ca^{2+} sensor for synaptic transmission, which resides in the synaptic vesicle membrane. Syt has two Ca^{2+} binding domains (►Calcium domain) and binds multiple Ca^{2+} ions.
CaMKII: A major constituent of ►postsynaptic density in excitatory synapses in the mammalian brain.

Characteristics

Ca^{2+} is a ubiquitous messenger and participates in a variety of cell functions in physiological and pathological conditions. The specificity of signal transmission is maintained by spatial and temporal localization of Ca^{2+} signals and Ca^{2+} binding proteins. At the synapse, Ca^{2+} plays crucial roles both in pre- and post-synaptic events. In each event, specialized Ca^{2+} binding proteins are involved. Among Ca^{2+} binding proteins at the synapse two proteins have been extensively studied. The role of a Ca^{2+} binding protein in the presynaptic terminal (►Presynaptic active zone), Synaptotagmin (Syt), is generally believed to be in detection of Ca^{2+} influx for synchronized fusion of ►synaptic vesicles (for review, [1,2]). Another Ca^{2+} binding protein, Ca^{2+}/Calmodulin-dependent protein kinase II (CaMKII) is abundant in the postsynaptic membrane and essential for plastic regulation of glutamate receptor channels (for review, [3]). There are many other Ca^{2+} binding proteins in neurons. Calbindin-D28K, calretinin and parvalbumin are distributed in specific neurons in the brain and considered to play a role as Ca^{2+} buffers. Calmodulin modifies channel functions and neuronal excitability, whereas Protein kinase C is involved in modulation of glutamate receptor channel functions and synaptic plasticity in the brain. ►Annexins are a family of Ca^{2+}- and phospholipid-binding proteins and bind to various presynaptic proteins such as rabphilin and synapsin. ►CAPS, Ca^{2+}-dependent activator protein for secretion, is an essential cytosolic component of the protein machinery involved in large dense-core vesicle exocytosis and in secretion of a subset of neurotransmitters.

In this essay, concentration will be on Syt in the presynaptic nerve terminal and CaMKII in the postsynaptic cell.

Synaptotagmin (Syt)

Electrical signals conveyed along an axon are converted into chemical signals at the synapse. The basic mechanism for synaptic transmission was established at the frog neuromuscular junction, about 50 years ago, by Katz and his collaborators [4]. Ca^{2+} plays the central role in this story. The electrical signal at the presynaptic terminal results in a transient influx of Ca^{2+} through voltage-gated Ca^{2+} channels, which is detected by a specialized Ca^{2+} sensor. Through a series of molecular interactions, this signal causes rapid fusion of synaptic vesicles and transmitter release. Among Ca^{2+} -binding proteins in the presynaptic terminal, Syt is the most promising candidate for the Ca^{2+} sensor.

Ca/Calmodulin-Dependent Protein Kinase II (CaMKII)

Synaptic transmission is malleable and plastic, which is believed to be the basis for memory and learning. Ca^{2+} again plays an important role in this process. CaMKII is

the major player among Ca^{2+} binding proteins in the postsynaptic side of the synapse. This kinase has been studied extensively in the mammalian central nervous system as it constitutes the postsynaptic density, and is intimately involved in ►long-term potentiation (LTP) of synaptic transmission in the brain.

Quantitative Description

Molecular Weight

Syt: ~65 kDa, probably works as an oligomer.

CaMKII, CaMKIIα, ~50 kDa and CaMKIIβ, ~60 kDa: Carboxy-terminal holoenzymes consisting of a stacked pair of hexameric subunit rings [5].

Higher Level Structures

Syt; Neurons, Endocrine and Exocrine cells, Presynaptic terminals, Synaptic vesicles, CaMKII; Mammalian brain, Hippocampus, Neurons, Synapses.

Lower Level Components

Syt: A major protein in the membrane of synaptic vesicles and ►dense core vesicles, which has an amino (N)-terminal transmembrane region followed by two C_2 domains (C2A and C2B). The C_2 domains are in the cytoplasm and uniquely situated to sense Ca^{2+} influx at the transmitter release site.

CaMKII: A major component in the postsynaptic density in the glutamatergic synapse.

Homologs

Syt: Syt includes 13 isoforms in humans, and by the database search, an additional six potential isoforms have been suggested. Although most Syt's are localized on transport vesicles, some (Syt III, VI, and VII) are present at the plasma membrane.

CaMKII, CaMKIIα, and CaMKIIβ are major isoforms in the brain.

Higher Level Processes

Syt: Inter-neuronal communication, regulation of hormone secretion.

CaMKII: Postsynaptic modulation of synaptic transmission, synaptic plasticity, memory and learning.

Lower Level Processes

Syt: ►Vesicle fusion, transmitter release.

CaMKII: Regulation of channel permeability and insertion of AMPA-type glutamate receptors in the postsynaptic density.

Process Regulation

CaMKII: Extensive synaptic activities translocate CaMKII from cytosol in the postsynaptic ►spines of dendrites to the postsynaptic density.

Function

Syt

Characteristics of the Ca^{2+} Sensor for Fast Synaptic Transmission

The Ca^{2+} sensor for ►fast synaptic transmission has the following characteristics: Synaptic potentials are steeply dependent on the Ca^{2+} concentration, indicating that multiple Ca^{2+} ions have to bind to the Ca^{2+} sensor for fast synaptic transmission. Furthermore, Ca^{2+} sensor for synaptic transmission is considered to have a low Ca^{2+} affinity. In a microdomain, the Ca concentration is considered to increase rapidly to high levels, since slow binding EGTA does not affect synaptic transmission but fast BAPTA does (but see review by Augustine et al. [6]). Since the Ca^{2+} sensor detects transient changes (sub-msec) of Ca^{2+} concentrations in the micro- or nanodomain, accurate determination of the Ca^{2+} concentration has been difficult. Two methods are suitable to estimate local Ca^{2+} concentrations. Caged Ca^{2+} can be released instantaneously by photolysis. Since caged Ca^{2+} compound can be equilibrated before photolysis, uncaged Ca^{2+} will distribute homogeneously in the presynaptic nerve terminal, and the Ca^{2+} concentration can be determined with a Ca^{2+} dye injected together with the caged Ca^{2+} compound. At the rat auditory synapse, calyx of Held, estimated values for release of transmitter are around 10 μM. Whereas, by using Ca^{2+}-sensitive K^+ channels localized close to presynaptic Ca channels as a probe for local changes of Ca^{2+} concentration, the peak concentration was estimated to be 175 μM (for review, [6]). Thus, the Ca^{2+} sensor for fast synaptic transmission has a relatively low affinity for Ca^{2+}. Syt is localized close to the release site and has multiple binding sites with low Ca^{2+} affinities. Thus, Syt is a good candidate for the Ca^{2+} sensor.

Functional Sites in Syt

Syt has multiple finding sides. Two Ca^{2+} binding domains, C2A and C2B, altogether have five putative Ca^{2+} binding sites. Among these binding sites, recent evidence indicates that C2B is the Ca^{2+} sensing domain for fast synaptic transmission (Fig. 1; [7]).

Oligomerization

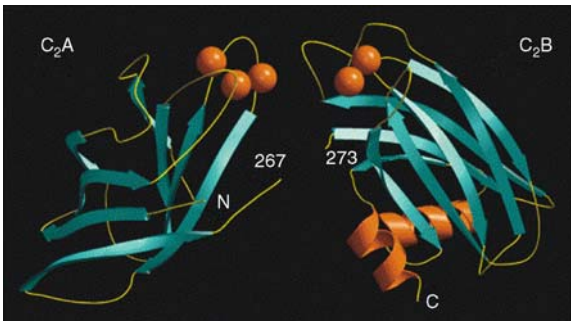
Syt oligomerizes Ca^{2+}-dependently. Whether this oligomerization is essential for vesicle fusion is a current issue. Ca^{2+}-dependent oligomerization occurs at C2B, and is conserved in all members of the Syt family.

Phospholipid Binding

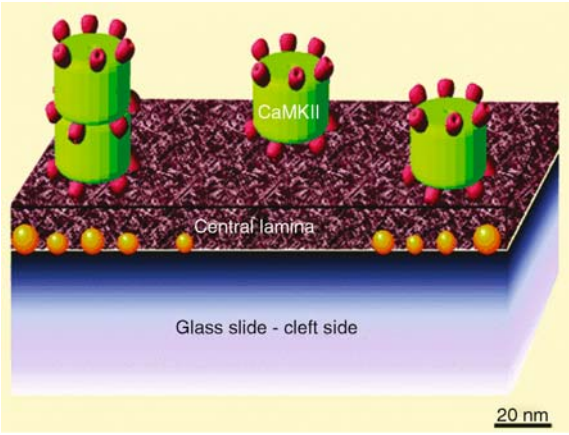
Syt binds phospholipids Ca^{2+} dependently, and this interaction is proposed to be a trigger for vesicle fusion.

Interaction with SNARE Complex

Syt also binds syntaxin 1, SNAP-25, Ca^{2+} channels, and AP-2. AP-2 is an adaptor protein for clathrin that is



Calcium Binding Proteins. Figure 1 Structure of Synaptotagmin I. C2A and C2B domains are oriented with their Ca^{2+} binding sites in a close proximity (reproduced from Fernandez et al. [7] with permission).



Calcium Binding Proteins. Figure 2 Diagram showing the structural relation between CaMKII and postsynaptic density (reproduced from Petersen et al. [8] with permission).

essential for endocytosis (for review [2]). Syt seems to be a multifunctional protein.

Phenotypes of Syt I-Null Mutations

Animals that lack Syt were generated in *Drosophila*, *C. elegans*, and mouse. Synaptic transmission in *Drosophila syt I*-null embryos, and in synapses formed in culture from neurons derived from *syt I*-null mouse embryos, have been studied. Nerve-evoked synchronous synaptic transmission is severely impaired, supporting the hypothesis that Syt I is a major Ca^{2+} sensor for fast synaptic transmission [2].

CaMKII (CaMKIIα and CaMKIIβ)

Localization

The postsynaptic density (PSD), an electron-dense structure directly apposed to the cytoplasmic face of the postsynaptic membrane, is prominent at excitatory glutamatergic synapses in the mammalian brain. CaMKII is a major protein in the PSD, and is specifically localized to the cytoplasmic face of PSD in a single layer, and in a highly ordered array of tower-like structures (Fig. 2; [8]).

This location of CaMKII is highly suited for detection of Ca^{2+} entering through NMDA-type glutamate receptor channels. CaMKII may be connected directly to ►NMDA receptor channels.

Phosphorylation

CaMKIIα and CaMKIIβ are contained in relatively high concentrations in brain tissue and phosphorylate non-specifically Ser and Thr residues in numerous proteins. CaMKII binding to NMDA receptors exposes CaMKII to high Ca^{2+} concentrations entering through the channels and induces autophosphorylation, which is necessary for induction of long-term potentiation (LTP). Once phosphorylated, CaMKII binds more tightly to the NMDA receptor channel and is persistently active, even after a fall in the Ca^{2+} level. This persistent activity then promotes enzymatic and structural processes that increase the number of AMPA-type glutamate receptor channels in the postsynaptic membrane.

Translocation During Synaptic Activities

Upon strong activation of NMDA receptor channels, CaMKII translocates to the PSD, where it can optimally detect Ca^{2+} entry through NMDA receptor channels and become phosphorylated. Under this condition, more ►AMPA receptor channels are recruited into the PSD [9]. By interaction with CaMKII, AMPA receptor channels also increase the single channel conductance. Both of these effects lead to potentiation of AMPA-mediated synaptic transmission.

Memory Impairments in CaMKII Knock-Out Mice

As described above, the involvement of CaMKII in LTP is convincing, however, it is yet to be established whether LTP is essential in memory acquisition in the animal. This was studied in CaMKIIα knock-out mice. In these mice, the hippocampus was deficient in LTP, although synaptic transmission was normal. These mice exhibit spatial learning impairments [10]. Thus, CaMKII plays an important role in the higher brain functions.

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Calcium/Calmodulin-dependent Protein Kinase II in Neurons

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Synonyms

CaM kinase II; CaMKII

Definition

Calcium(Ca^{2+})/►calmodulin-dependent protein kinase II, or CaMKII, is a multifunctional serine-threonine ►kinase highly abundant in the brain (1–2% of all proteins). The enzyme is activated by the binding of the complex Ca^{2+}-calmodulin (CaM). The hallmarks of CaMKII are its unique structural and regulatory properties, which endow the enzyme with the ability to decode the spatial and temporal patterns of Ca^{2+} signals. As such, the enzyme is well equipped to control multiple functions in nerve cells via the ubiquitous Ca^{2+} signaling systems. CaMKII is particularly abundant in the ►post-synaptic density (PSD), accounting for its important role in synaptic plasticity and some forms of learning and memory. This essay is an overview of the structure and regulation of CaMKII followed by some examples of how the unique features of the enzyme support its ability to serve as a major decoder of neuronal activity. Finally, a particular focus is made on the important role of CaMKII in regulating glutamatergic synapses of the ►hippocampus, because, ►synaptic plasticity and the implication of CaMKII have been extensively studied in this brain region.

Characteristics

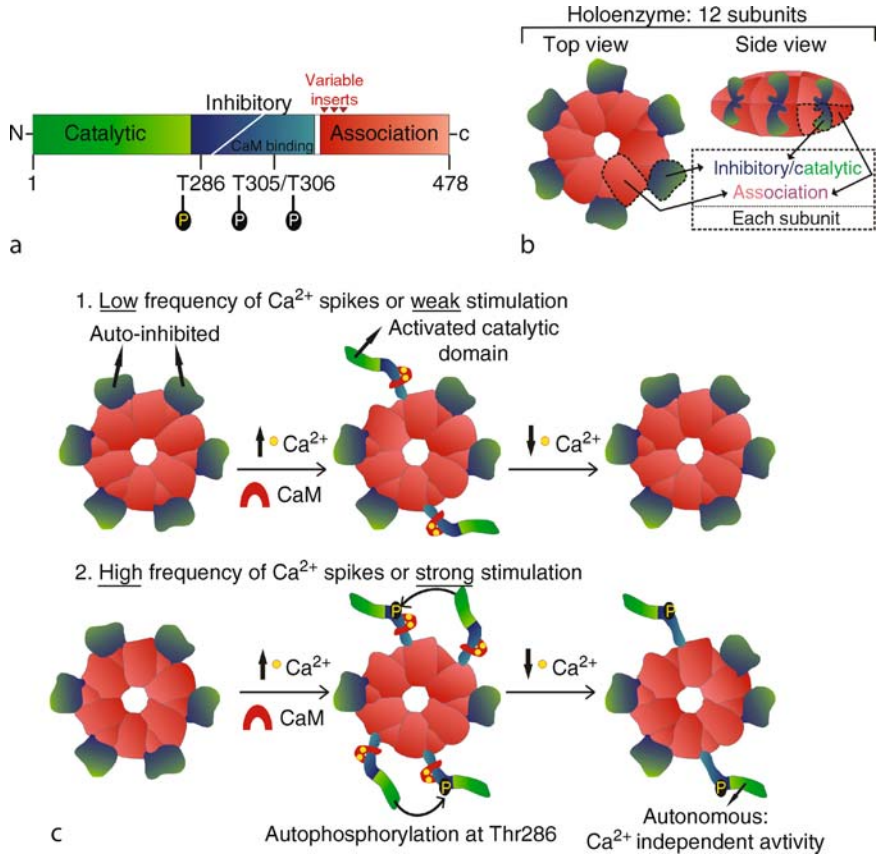
Structure and Regulation of CaMKII

The CaMKII family is encoded by four different genes α, β, δ and γ, from which at least 28 isoforms can be derived. The gene encodes for three principal domains in the protein: catalytic, autoinhibitory and association domains. In the brain, the α and β genes are predominantly expressed. In the cell, the enzyme is not expressed as a single protein, but rather as a homo- or heteromeric complex (holoenzyme) of 12 subunits. The 12 catalytic and regulatory domains form 2 hexameric rings on each side of a central core comprising 12 association domains (Fig. 1).

The catalytic domain is not only responsible for substrate phosphorylation, it also supports the binding of the enzyme to various proteins. Under basal conditions, the autoinhibitory domain keeps its counterpart catalytic domain inactive [1–3]. The structure of both the catalytic and regulatory domains of CaMKII, in its autoinhibited conformation, has been recently determined by crystallography, revealing that the regulatory segments of two subunits form a dimeric structure that blocks ►ATP and substrate binding to the catalytic domain [3]. Following a rise in intracellular Ca^{2+}, Ca^{2+}-bound CaM (Ca^{2+}/CaM) molecules bind to the autoinhibitory domain of individual kinase subunits thereby activating them by relieving their inhibition.

CaMKII as a Molecular Memory

CaMKII activity is regulated by Ca^{2+}/CaM binding, but also by phosphorylation. Binding of Ca^{2+}/CaM not only activates each kinase subunit, but also exposes an important amino acid for their regulation: Thr286 (for α isoforms, Thr287 for β isoforms). This amino acid on one subunit can be phosphorylated by a neighboring catalytic domain from another subunit in the holoenzyme, a process termed autophosphorylation. Autophosphorylation at Thr286, residing in the autoinhibitory domain, switches the kinase subunit to an autonomous, Ca^{2+}-independent state. Thus, once Ca^{2+} levels in the cell have returned to baseline, the phosphorylated subunits remain active despite the eventual dissociation of Ca^{2+}/CaM, which itself is also slowed down 10,000 fold. As such, Thr286 phosphorylation is considered a biochemical memory of a previous rise in Ca^{2+}.



Calcium/Calmodulin-Dependent Protein Kinase II in Neurons. Figure 1 Structure of CaMKII.
(a) Primary structure of CaMKII domains. (b) Model structure of CaMKII dodecamer. (c) Model of CaMKII activation by Ca^{2+} spikes [1,3].

Following Thr286 phosphorylation and Ca^{2+}/CaM dissociation, a second autophosphorylation can occur at Thr305/306, located in the Ca^{2+}/CaM binding domain. But in opposition to Thr286, this phosphorylation blocks subsequent Ca^{2+}/CaM binding, preventing those subunits from being activated [1,2]. Thus, phosphorylation allows for a bi-directional control of CaMKII activity.

In addition to activating CaMKII, Ca^{2+}/CaM binding and phosphorylation at Thr286 expose binding sites on the enzyme for interactions with other proteins. One example of such activity-dependent interactions at synapses is with the N-Methyl-D-Aspartate ►(NMDA) receptor, particularly the NR2B subunit. The binding of NR2B to activated CaMKII also leads to a similar form of biochemical memory because it prevents the autoinhibitory domain from flipping back on the catalytic region, thereby leading to autonomous activity of CaMKII [4]. The interesting distinction for this form of CaMKII autonomy, in comparison to the classical autophosphorylation-dependent autonomy, is that it cannot be reversed by ►phosphatase activity. Furthermore, this binding interaction between CaMKII and NR2B can switch to a persistent mode after a strong Ca^{2+}/CaM activation [4,5], providing a long-lasting form of molecular memory that is ideally suited to sustain ongoing changes in synaptic biochemistry.

CaMKII as a Decoder of Calcium Oscillations

The rules governing Thr286 phosphorylation of individual subunits within CaMKII dodecamers make the enzyme capable of decoding the number and frequency of Ca^{2+} spikes. The Thr286 phosphorylation reaction can occur only between two neighboring subunits that have been coincidently activated by Ca^{2+}/CaM binding (Fig. 1c). If exposed to brief Ca^{2+} spikes, as seen at ►excitatory synapses, the dual binding of Ca^{2+}/CaM to neighboring subunits has a low probability. Upon repetitive spikes, the probability of coincident binding of Ca^{2+}/CaM increases, but only if the spike intervals are sufficiently brief to favor accumulation of bound Ca^{2+}/CaM on the holoenzyme. Thus, above a steep threshold frequency of Ca^{2+}

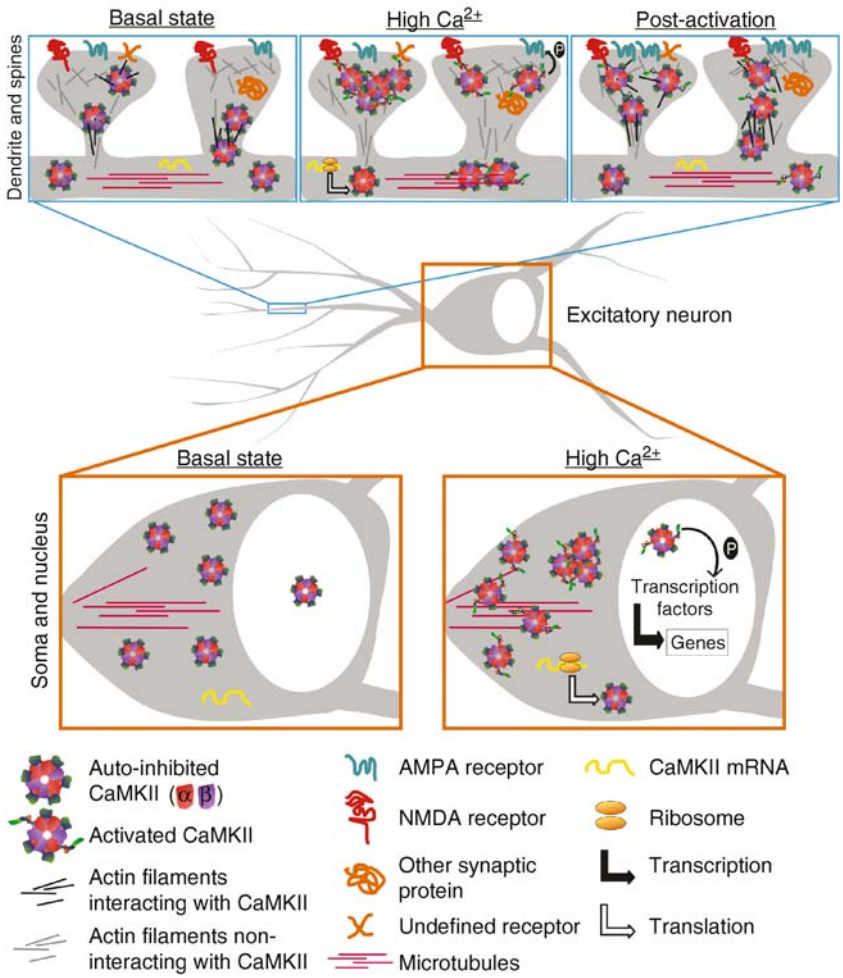
oscillations, the number of phosphorylated subunits per holoenzyme increases over time. The differential accumulation of phosphorylated – or autonomous – subunits in a CaMKII dodecamer encodes the number and frequency of Ca^{2+} oscillations. The initial fraction of autophosphorylated subunits in CaMKII, the amplitude and duration of individual Ca^{2+} spikes and the affinity of different CaMKII subtypes for CaM have all been shown to modulate the frequency response of the enzyme [6]. These remarkable features should allow the enzyme to decode the temporal patterns of neuronal activity.

Spatiotemporal Regulation of CaMKII

Specificity in signaling is also achieved by controlling the subcellular location of molecules. The subcellular localization of CaMKII is highly regulated by Ca^{2+}. Thus, in response to synaptic or electrical activities, the enzyme translocates rapidly to various neuronal compartments, where it can act on diverse functions. (Fig. 2).

Different subunits, such as α and β, bind to common as well as different targets. These subunits can co-assemble in various ratios within dodecamers, allowing the enzyme to be recruited to an increased number of sites in the cell [1,7]. Among the multiple sites that CaMKII can probably translocate to, only a few have been characterized, as described below.

Nucleus: Because of its large multimeric structure, CaMKII cannot enter the nucleus by passive diffusion. However, the kinase has been detected by immunocytochemistry in the nucleus of a variety of cell types. The enzyme thus needs a nuclear localization signal (NLS) or a binding partner that contains one to enter the nucleus. In the brain, only the splice variant α_B-CaMKII



Calcium/Calmodulin-Dependent Protein Kinase II in Neurons. Figure 2 Multiple sites of CaMKII targeting and activity-dependent translocation in neurons.

contains a functional NLS. But αKAP, a CaMKII anchoring protein that is derived from the α gene, also contains an NLS. αKAP lacks the catalytic and regulatory domains but contains the association domain. It can thus form holoenzymes with other CaMKII isoforms and can target them to the nucleus. Indeed, only 1 or 2 subunits per holoenzyme are necessary for nuclear translocation of the dodecamer. Functionality of the NLS is also regulated by phosphorylation. For example, autophosphorylation at Thr286 affects its nuclear translocation [1,7].

Membranes: αKAP contains an N-terminal hydrophobic sequence instead of the standard N-terminal kinase domain. This can support the recruitment of the enzyme to intracellular membranes, like to the sarcoplasmic reticulum in skeletal muscle [7].

Cytoskeleton: In their non-activated state, β-CaMKII binds to ►F-actin whereas α-CaMKII is predominantly cytosolic. Following activation, β-CaMKII unbinds actin and both subunits can bind to other cytoskeletal components, like ►microtubules. Microtubule-associated proteins, such as Tau, MAP2 and MAP6 are major substrates for CaMKII [1,2].

Synapses: CaMKII can translocate to postsynaptic sites during neuronal activity, where the kinase can also bind to several synaptic proteins. Its multivalent structure should in fact allow CaMKII to simultaneously bind several partners (Fig. 2). This is particularly relevant in the PSD, where proteins are tightly packed (hence the electron-dense nature) and where CaMKII is particularly abundant. One major activity-dependent binding target of CaMKII at synapses is the NMDA receptor, as described above. This interaction is of particular interest because it can be made persistent above a certain activation threshold, and may lock the enzyme at stimulated synapses [5].

In addition, the ►messenger RNA (mRNA) of α-, but not β-CaMKII, is transported in dendrites in an activity-dependent manner, where local translation can occur. This enables a rapid and localized delivery of CaMKII proteins to synapses [8]. At presynaptic sites, CaMKII is associated with synaptic vesicles and can bind and phosphorylate ►synapsin I [2].

Intracellular clustering: During ischemia, or during strong stimulation at synapses, CaMKII holoenzymes bind to each other. This process called self-association forms supramolecular aggregates of holoenzymes. Those inter-holoenzyme interactions, which are formed via catalytic and autoinhibitory domains, need activation of the kinase by Ca^{2+}/CaM and are regulated by intracellular pH, ATP concentration and autophosphorylation. Aggregates of CaMKII have been observed in vitro as well as in intact cells, both at synaptic and extrasynaptic sites [1,9]. This process could favor additional recruitment of CaMKII at strongly stimulated synapses and might support the formation of post-synaptic scaffolds embedded with multiple CaMKII and binding partners.

CaMKII and Neuronal Function

CaMKII is implicated in various cellular functions, including the regulation of carbohydrate metabolism, membrane current, ►neurotransmitter synthesis and release, cytoskeletal organization, intracellular Ca^{2+} homeostasis, ►transcription, synaptic plasticity and some forms of memory [1]. Here, we will focus on CaMKII implications in gene regulation and synaptic plasticity.

CaMKII and Gene Regulation

During neuronal activity, Ca^{2+} levels increase in the cytosol, but also in the nucleus. The ability of some isoforms of CaMKII to target the nucleus suggests that the enzyme is involved in regulating gene expression. CaMKII can phosphorylate ►transcription factors, like CREB, ATF-1 and NeuroD, and is known to regulate the transcription of the immediate-early gene *c-fos*. To date however, most evidence showing that CaMKII regulates gene expression comes from studies in non-neuronal systems. For example, the first experimental evidence that nuclear localization of CaMKII was required for transcriptional regulation was shown for the gene coding for atrial natriuretic factor in heart tissue [1,7,8].

CaMKII and Synaptic Plasticity; Learning and Memory

CaMKII has attracted the attention of neuroscientists in particular because of its role in synaptic plasticity, learning and memory. Studies have been done mostly in the hippocampus, but results from other regions also support the role of CaMKII in synaptic plasticity. Long-term potentiation (LTP) of synaptic transmission is a type of synaptic plasticity that is thought to underlie some forms of learning and memory. Several results indicate that CaMKII, activated by the rise in Ca^{2+} that accompanies the high-frequency stimulation required to induce LTP, initiates a biochemical cascade that potentiates synaptic transmission. Indeed, after the induction of LTP, autonomous activity of CaMKII increases. Peptide inhibitors blocking both Ca^{2+}-dependent and -independent activity of CaMKII prevented LTP induction by different protocols. But because of the possible lack of specificity of these inhibitors, the essential role of CaMKII in LTP was only confirmed after the observation of an impaired synaptic potentiation in αCaMKII knockout mice and in mice that express a mutant CaMKII that cannot autophosphorylate at Thr286. Those mice also show deficits in both learning and memory. For instance, preventing CaMKII autophosphorylation was shown to interfere with experience-dependent plasticity, such as spatial

learning. Local translation of αCaMKII in dendrites is also important for synaptic plasticity because disrupting the transport of its mRNA impairs LTP and some types of memory. Conversely, instead of inhibiting or removing CaMKII, introducing activated CaMKII in neurons of hippocampal slices can induce LTP [8,10].

How does CaMKII regulate synaptic transmission? Many mechanisms have been examined, but one good example is its effects on ►AMPA receptors. CaMKII phosphorylates these synaptic receptors, thereby enhancing their conductance, and also leads to the addition of new AMPA receptors into synapses. Both effects contribute to strengthening the synapse [8,10]. But in addition to its signaling effects, CaMKII seems to play a structural role in synaptic plasticity. A recent study demonstrated that β-CaMKII, but not α, was capable of bundling F-actin, independently of its kinase activity. This bundling stabilizes the architecture of dendritic spines and might support dendritic spine remodeling that accompany synaptic plasticity.

Summary

CaMKII is a multifunctional kinase highly abundant in the brain and critically involved in the regulation of several functions in neurons. Its unusual structural and regulatory properties support its multiple functions by enabling the enzyme to decode specific patterns of Ca^{2+} signals in time and in space, for brief and long-lasting effects. Since the discovery of CaMKII by Howard Schulman and colleagues three decades ago, many studies have unraveled some of its functions and mechanisms of action, but many aspects are still unresolved. Nevertheless, what we have learned so far about this enzyme has contributed to a better understanding of how signaling in cells can be achieved with specificity, multiplicity, efficiency, and persistence.

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Calcium Channel Blocker

Definition

A family of clinically used compounds that block the L-type Cav1.2 calcium channel and relaxes smooth muscle.

Calcium Channelopathies

Definition

One type of ion ►channelopathies leading to neurological disorders in vertebrates including humans. Since rises in intracellular Ca^{2+} concentration $[Ca^{2+}]_i$ regulate or initiate a plethora of intracellular events including metabolic processes, secretion of ►neurotransmitters and hormones, muscle contraction, cell differentiation and gene expression, and since these $[Ca^{2+}]_i$ rises are largely generated by influx into the intracellular medium via ►voltage-gated L-type Ca^{2+} channels, genetic dysfunctions of these channels cause multifarious neurological diseases, including ►hypokalemic periodic paralysis (loss of muscle strength), failures in muscle ►excitation-contraction coupling, ►migraine, ►ataxia, congenital stationary night blindness, or malignant hyperthermic sensitivity.

►Ataxia
►Hypokalemic Periodic Paralysis
►Migraine

Calcium Channels – An Overview

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Definition

►Voltage-gated Ca^{2+} channels are integral membrane proteins forming aqueous pores which open in response to cell depolarization. Ca^{2+} channels play a key role in controlling vital functions: they shape the ►action potential and membrane electrical oscillations and act as gate-controller of Ca^{2+}, the most ubiquitous ►second messenger [1]. As such, Ca^{2+} channels are implicated in cardiac, skeletal and smooth ►muscle contraction (►excitation-contraction coupling), ►hormone and neurotransmitter release (►excitation-secretion coupling) and Ca^{2+}-dependent processes that modulate short- and long-term cell activity and gene expression (►excitation-transcription coupling) [2–5].

Characteristics

Ca^{2+} channels have been grouped into two main classes, based on their threshold of activation: the ►high voltage-activated (HVA) channels and the ►low voltage-activated (LVA) channels [4]; although this classification could not be strictly applied since some of the HVA channels activate at significantly low voltages [2]. LVA channels activate " ►transiently" during small depolarizations near ►resting membrane potentials (→ ►Membrane potential – basics) and are therefore commonly indicated as T-type channels. T-type channels are responsible for ►low-threshold spikes, oscillatory cell activity, muscle contraction, hormone release, cell growth, differentiation and proliferation [5]. The HVA channels require larger membrane depolarizations to open and are further subdivided into four types (►L-, N-, P/Q- and R-type $Ca^{2\pm}$ channels) based on their structural, pharmacological and biophysical characteristics [2,3]. They are responsible for the sustained depolarizing phase of action potentials, muscle contraction, hormone and neurotransmitter release, gene expression and cell differentiation.

Molecular Structure

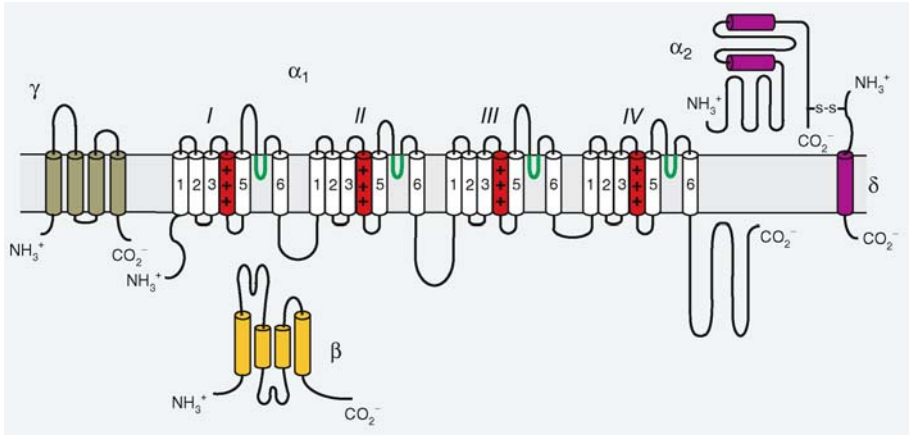
The principal pore-forming subunit of both LVA and HVA channels is the α_1-subunit, a high- molecular weight protein (190–250 kDa), which is structurally similar to the ►$Na^{\pm}$ channel α-subunit [1]. It is formed by four domains (*I–IV*) linked together in a single polypeptide chain and each domain contains six putative transmembrane segments (S1–S6), plus a loop (P) that dips partially into the pore to form the pore-lining region (Fig. 1). The cytoplasmic loops linking the four domains are structurally important for their interactions with β-subunits, second messengers, membrane binding proteins and channel ►gating.

Molecular cloning of Ca^{2+} channels has provided evidence for the existence of ten different pore-forming α_1 subunits with pharmacological and biophysical profiles similar to the endogenous Ca^{2+} channels expressed in most tissues. Alignment of their amino acid sequences suggests strong homologies and divergences between the various Ca^{2+} channel types (Fig. 2). Strong homologies exist between the four L-types (Cav1), the N-, P/Q- and R-type (Ca_v2), and the three T-type (Ca_v3) channels, while large divergences exist between the HVA and LVA subfamilies. Figure 2 reports the Ca^{2+} channel classifications most used in the literature [2,3].

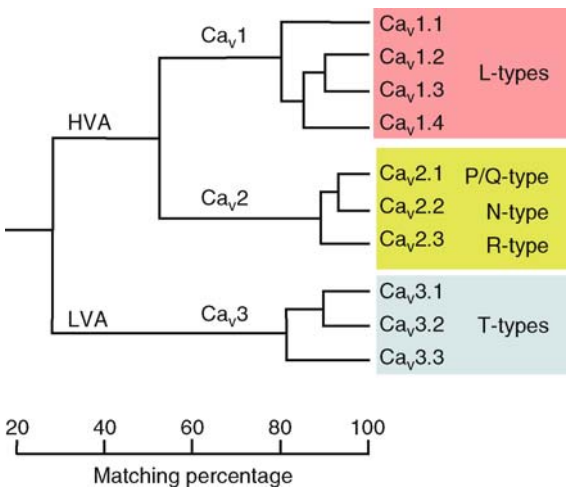
At variance with the T-type channels, whose α_1-subunit is sufficient to warrant ►activation and ►inactivation gating, channel expression and membrane incorporation, the HVA channels are hetero-multimeric protein complexes which comprise the α_1-subunit in association with auxiliary β, α_2-δ and γ-subunits (Fig. 3). Coexpression of α_2-δ with the α_1-subunit ensures proper Ca^{2+} current kinetics and current densities. The same occurs with the co-expression of β and α_1-subunits. Still vague is the role of γ-subunits (γ_1 to γ_8) which consist of four transmembrane domains and whose site of interaction with the α_1-subunit is still unknown. The α_2-δ-subunit is formed by a membrane-spanning δ-peptide (27 kDa) and an extracellular α_2-peptide (143 kDa) bound together by a disulfide bridge (Fig. 1). Presently, four genes encoding for different α_2-δ-subunits (α_2-δ_1 to α_2-δ_4) have been identified with several additional splice variants. The up-regulation of the α_2-δ gene appears to correlate with the onset of ►allodynia (non-noxious stimuli eliciting pain) and ligands that target the α_2-δ-subunit, the gabapentins, are used for treatment of neuropathic pain. The four β-subunits (β_1 to β_4) and their splice variants so far identified are almost exclusively cytosolic. They possess a hydrophobic region containing SH3 and guanylate kinase domains, indicating that they belong to the membrane-associated guanylate kinase (MAGUK) family and as such may integrate multiple signaling pathways near the channel. The β-subunit has high-affinity for a conserved region within the domain I-II region of N- and PQ-type channels, termed the *alpha interaction domain* (AID).

Activation-Inactivation Gating

As for other voltage-gated ion channels, the probability of Ca^{2+} channels opening is strictly voltage-dependent, i.e., the switch from a closed (non-conductive) to an open (conductive) configuration is strictly dependent on voltage, usually requiring 4–8 mV to change e-fold the probability of channel opening [6]. Structure-function



Calcium Channels – An Overview. Figure 1 Subunit structure of voltage-gated Ca^{2+} channels: transmembrane topology of the α_1 and associated auxiliary subunits (β, α_2-δ, γ). Predicted α-helices are depicted as cylinders. For the α_1-subunit the transmembrane spanning α-helices (1 to 6) are repeated in the four domains (*I* to *IV*). Red cylinders indicate the positively charged S4 segments (voltage sensors), and the thick green lines denote the pore loops (P) that line the permeation pathway for Ca^{2+}. The lengths of lines are not intended to represent the exact lengths of the polypeptide segments indicated. The same is for the size of various subunits. Adapted and redrawn from ref [2].



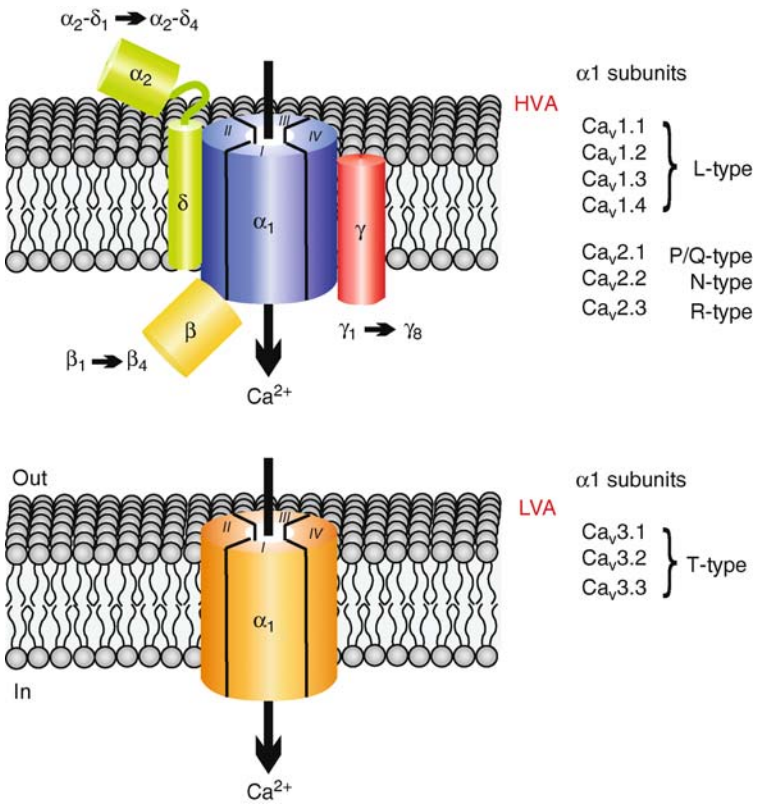
Calcium Channels – An Overview.
Figure 2 Phylogenetic tree of voltage-gated Ca^{2+} channels, showing the percentage of identity between the different cloned Ca^{2+} channels [5]. The first bifurcation occurs between HVA and LVA channels. The HVA family includes four genes encoding the L-type channels ($Ca_v1.1$–$Ca_v1.4$) and three genes encoding the P/Q ($Ca_v2.1$), N- ($Ca_v2.2$) and R-type ($Ca_v2.3$) channels. The LVA family includes three genes encoding the $Ca_v3.1$–$Ca_v3.3$ channels. Adapted and redrawn from ref [5].

studies have associated this property to the presence of positively charged lysine and arginine residues distributed in the S4 transmembrane segment of each domain, which form the " ►voltage sensor " (Fig. 1). However, the exact location of the activation gates that regulate the open and closed states of the pore remains unknown.

During maintained depolarization, Ca^{2+} channels tend to inactivate, but the speed and extent of channel inactivation may vary dramatically. In general, Ca^{2+} channels inactivate by either Ca^{2+}- or voltage-dependent mechanisms. Ca^{2+} -dependent inactivation is dominant for the cardiac $Ca_v1.2$ L-type channel, but may also occur for other HVA channels. ►Ca^{2+}-dependent inactivation is a ►calmodulin-dependent process, involving sites on the C-terminal domain of the α_1-subunit. Voltage-dependent inactivation is a general term for inactivation that does not clearly depend on Ca^{2+}. ►T-type Ca^{2+} channels tend to inactivate rapidly and almost completely, while inactivation of HVA channels is usually slow and incomplete. Spontaneous switch between inactivating and non-inactivating modes have been observed in single N-type channels, perhaps reflecting modulation by some intracellular signaling process. However, how Ca^{2+}-binding or membrane voltage affect the inactivation gate is still widely unknown [6].

Channel Permeability

The present view of Ca^{2+} channel permeability is based on the existence of an intrapore binding site controlling both ion selectivity and channel block: the ►selectivity filter. This highly specialized region of Ca^{2+} channels consists of a ring of four negative charged groups inside the pore. In HVA channels, each of the four P loops contains a glutamate forming the EEEE locus, in T-type channels two glutamates are substituted by two aspartates in the corresponding position (EEDD locus). The spatial arrangement of the four negative charges



Calcium Channels – An Overview. Figure 3 Schematic representation of the voltage-gated Ca^{2+} channel complex. On top is represented the heteromeric structure of the HVA Ca^{2+} channel, consisting of the pore forming α_1-subunit (with the four domains *I* to *IV*) plus the β, γ and α_2-δ auxiliary/regulatory subunits. To the bottom is represented the LVA Ca^{2+} channel consisting only of the pore forming α_1-subunit. To the right are listed the different α_1-subunits that correspond to different Ca^{2+} channel isoforms. Adapted and redrawn from ref [3].

in the P loops is postulated to closely coordinate two Ca^{2+} ions whose sequential entrance and subsequent interaction induce high Ca^{2+} fluxes while preserving high affinity for the pore-site [7]. Although this simple ion-ion interaction would explain the dual nature of Ca^{2+} as permeant ions at millimolar concentrations and as blockers of Na^{+} currents at micromolar concentrations, the complete understanding of Ca^{2+} channel permeability is likely to require a further hypothesis of ion-pore structure interactions. The recent availability of T-type channel clones [5] has allowed closer comparisons between LVA and HVA channel permeability properties, highlighting the role that the EEEE or EEDD locus play in the regulation of ion selectivity in the two channel groups. $Ca_v3.1$ T-type channels have apparently a narrower pore size (5.1 Å diameter) compared to the $Ca_v1.2$ L-type pore size (6.2 Å diameter) [7]. This structural difference may explain the different Ca^{2+}/Ba^{2+} selectivity and blocking action of Cd^{2+} and Ni^{2+} of the two channel families (LVA and HVA): the L-, N- and P/Q-type channels being more permeable to Ba^{2+} than Ca^{2+} and more sensitive to the block by Cd^{2+} and the T-type channels being equally permeable to Ca^{2+} and Ba^{2+} and more sensitive to the block by Ni^{2+} (Table 1).

Physiology, Pharmacology and Channelopathies

In the following paragraphs are described the tissue and cellular location, physiological role, pharmacology and related ►channelopathies associated to each Ca^{2+} channel type as summarized in Table 1.

L-type channels (Ca_v1). L-type channels are widely expressed in many tissues and control a number of Ca^{2+}-dependent responses in excitable cells. In central neurons they are preferentially located on proximal dendrites and cell bodies and are involved in postsynaptic integration, neuronal plasticity, gene transcription and mood behavior. In sensory neurons (►cochlear hair cells and photoreceptors), they directly control neurotransmitter release and sensory perception. The L-type family includes four α_1-subunits ($Ca_v1.1$ to $Ca_v1.4$) with different structure-function characteristics but common blockers: ►1,4-dihydropyridines (DHPs), ►phenylalkylamines and ►benzothiazepines. With the exception of $Ca_v1.3$ and $Ca_v1.4$, which activate at

Calcium Channels – An Overview. Table 1 Selective and often used blockers, distribution and established channelopathies [10] of the various voltage-gated Ca^{2+} channels

Channel		Blockers		Distribution	Channelopathies	
		Selective	Unselective (often used)		Gene	Diseases
L	$Ca_v1.1$	Dihydropyridines, phenylalkylamines, benzothiazepines	Cd^{2+}	Skeletal muscles, transverse tubule	CACNA1S	Hypokalemic periodic paralysis & malignant hyperthermia in humans, muscular dysgenesis in mice
	$Ca_v1.2$	Dihydropyridines, phenylalkylamines, benzothiazepines	Cd^{2+}	Cardiac & smooth muscle myocytes; endocrine cells, neuronal cell bodies & dendrites	CACNA1C	Timothy syndrome
	$Ca_v1.3$	Dihydropyridines, phenylalkylamines, benzothiazepines	Cd^{2+}	Endocrine cells; neuronal cell bodies & dendrites, atrial myocytes & pacemaker cells, cochlear hair cells	CACNA1D	Deafness, sinoatrial & atrioventricular node dysfunction
	$Ca_v1.4$	Dihydropyridines, phenylalkylamines, benzothiazepines	Cd^{2+}	Retinal rod & bipolar cells, spinal cord, adrenal gland, mast cells	CACNA1F	Congenital stationary night blindness type 2, X-linked cone-rod dystrophy type 3
P/Q	$Ca_v2.1$	ω-agatoxin IVA	Cd^{2+}	Nerve terminals & dendrites, neuroendocrine cells	CACNA1A	Episodic ataxia type-2, spinocerebellar ataxia type-6, familial hemiplegic migraine
N	$Ca_v2.2$	ω-conotoxin VIA, SNX 111 (ziconotide)	Cd^{2+}	Nerve terminals & dendrites, neuroendocrine cells	CACNA1B	
R	$Ca_v2.3$	SNX 482	Cd^{2+}, Ni^{2+}	Nerve terminals & dendrites, neuroendocrine cells, cardiac myocytes	CACNA1E	
T	$Ca_v3.1$	none	Ni^{2+}, mibefradil	Neuronal cell bodies & dendrites, cardiac & smooth muscle myocytes	CACNA1G	
	$Ca_v3.2$	none	Ni^{2+}, mibefradil	Neuronal cell bodies & dendrites, cardiac & smooth muscle myocytes, neuroendocrine cells	CACNA1H	Childhood absence epilepsy
	$Ca_v3.3$	none	Ni^{2+}, mibefradil	Neuronal cell bodies & dendrites	CACNA1I	

relatively low voltages, the other Ca_v1 channels activate at voltages much more positive than resting potential. Activation is fast and sharply voltage-dependent while inactivation is relatively slow in the presence of Ba^{2+} but speeds-up in the presence of Ca^{2+} (►Ca^{2+}-dependent inactivation). Deactivation (giving rise to ►tail currents) is also fast, ensuring rapid closing of the channels on membrane repolarization to resting levels. L-type channels are distinguished from the other Ca_v channels by their high sensitivity to DHPs. DHP antagonists (nifedipine, nitrendipine) reversibly block the channels and help quantifying the amount of L-type channels expressed in a cell, while DHP agonists (Bay K 8644) prolong the open state of the channel, producing slow tail currents near resting potential. As such, DHP agonists allow measuring the ►single channel activity of high conductance L-type channels in membrane patches, otherwise hardly detectable [8]. L-type channels can be often distinguished from the other Ca^{2+} channels for their ►cAMP/PKA-mediated up-regulation which causes increased mean open times and probability of openings at the single channel level and increased Ca^{2+} current amplitude in whole-cell recordings [9]. Neuronal and neuroendocrine L-type

channels can be also inhibited by a fast ►G-protein coupled receptor (GPCR) mechanism activated by neurotransmitters which could be at the basis of an ►autocrine feedback control of hormone release.

P/Q-type channels ($Ca_v2.1$). The $Ca_v2.1$ family includes two Ca^{2+} channels which are nearly indistinguishable except for their different affinity to a common blocker: the spider venom ω-agatoxin IVA. P-type channels are more sensitive to ω-agatoxin IVA (K_d 1–3 nM) than Q-type channels (K_d 100–200 nM). $Ca_v2.1$ channels are widely expressed in neurons but are also available in pancreatic, pituitary and chromaffin cells. Their main physiological function is to control neurotransmitter release in central neurons and mammalian ►neuromuscular junctions where they are highly expressed at the presynaptic sites. P/Q-type channels control also the excitation-secretion coupling in pancreatic and chromaffin cells. $Ca_v2.1$ channels play a key role in neurotransmitter release due to their high-density of expression at the release sites of central synapses and share most of the modulatory properties of N-type channels described below. Similarly to the N-type channels they bind tightly to the ►SNARE complex proteins at the ►synprint motif of the II-III linker of the channel. P/Q-type channels are also effectively inhibited by the neurotransmitter activated GPCRs mechanism described below. Missense mutations of P/Q-type channels cause ►familial hemiplegic migraine (FHM) associated to an apparent gain of function as a result of an increased probability of channel openings and alteration of synaptic transmission (Table 1).

N-type channels ($Ca_v2.2$). $Ca_v2.2$ channels are widely expressed in the central and peripheral nervous system and chromaffin cells. They are highly expressed at the nerve terminals, where they control neurotransmitter release, and to a minor degree at the dendritic sites, where they are involved in Ca^{2+} signaling. $Ca_v2.2$ channels control also hormone release in neuroendocrine cells. The channels activate at relatively high voltages. Maximal activation at positive potentials and deactivation on return to resting levels are both fast. Inactivation is variable but significantly faster than L-type channels and slower than T-type channels. $Ca_v2.2$ channels are insensitive to DHPs but are selectively blocked by ω-conotoxin GVIA and related cone snail toxins (Table 1).

N-type channels play a key role in neurotransmitter release due to their high-density of expression at the release sites and their tight binding to the SNARE complex of the vesicle release machinery (syntaxin 1A, SNAP-25, VAMP2/synaptobrevin and synaptotagmin). These proteins bind at the synprint motif of the II-III linker of the channel and the tight interaction affects the availability and gating of the channel. The SNARE complex in fact either steadily inactivates the channel or inhibits its activation through a $G_{\beta\gamma}$ subunit. Interestingly, N-type channels are effectively modulated by GPCRs activated by neurotransmitters and the mechanism is thought to be at the basis of ►presynaptic inhibition. Briefly, an activated $G_{\beta\gamma}$ subunit binds directly to the pore-forming α_1-subunit of the N-type channel and shifts the gating mode from "willing" (from which the channel readily opens) to "reluctant" (from which the channel opens less frequently). The ►modulatory mechanism is ►membrane-delimited, voltage-dependent and causes an increased delay of the channel opening which produces an overall slow activation of the "reluctant" channel. Strong depolarizations opening the channels reduce the affinity of $G_{\beta\gamma}$ for the α_1-subunit and the channel recovers its normal gating mode.

R-type channels ($Ca_v2.3$). $Ca_v2.3$ channels are widely expressed in the central nervous system at the cell bodies, dendrites and presynaptic terminals. They are also expressed in ►motoneurons, heart, pituitary and chromaffin cells. The $Ca_v2.3$ channel has been originally reported to encode a Ca^{2+} channel type with biophysical properties between LVA and HVA channels, or usually as an HVA channel resistant to DHPs, ω-toxins and thus called R-type (for "residual"). Ca_v3 channels are likely to form a family of several channels with fast activation but variable inactivation that could be fast and comparable to the Ca_v3 types or slow like the Ca_v1 channels. They are involved in neurotransmitter and hormone release, repetitive firing (→ ►Action potential) and ►long-term potentiation. The tarantula toxin SNX-482 blocks exogenously expressed $Ca_v2.3$ currents but is only partially or not effective on native R-type currents, suggesting that $Ca_v2.3$ does not always conduct a significant portion of the R-type current which remains after blocking all the other ►voltage-gated Ca^{2+} channels. $Ca_v2.3$ channels are also sensitive to small doses of Ni^{2+}. In some case the Ni^{2+} block has K_d comparable to that of the $Ca_v3.2$ T-type channel described below.

T-type channels (Ca_v3). Ca_v3 channels ($Ca_v3.1$ to $Ca_v3.3$) are ubiquitously expressed and sustain key physiological functions which derive from their unique properties [4,5]: (i) they activate and inactivate at unusually negative voltages and are responsible for a window-current near resting potentials, (ii) they exhibit fast and complete inactivation during sustained depolarization and deactivate slowly on repolarization, (iii) they are equally or slightly more permeable to Ca^{2+} than Ba^{2+} and have small single channel conductance, (iv) they outlast ►membrane-patch excision and (v) they are preferentially blocked by low doses of mibefradil and Ni^{2+} (particularly the $Ca_v3.2$) (Table 1). At present, Ca_v3 channels are recognized to play a critical role in many physiological functions in which a low-threshold Ca^{2+} entry is required to trigger, or sustain, specific cell activities. This is particularly true for the generation of low-threshold spikes, pacemaking activity, hormone

secretion, cell growth and differentiation. T-type channels play also a critical role in several pathologies in which either their recruitment, overexpression, or altered gating cause cardiac hypertrophy, hypertension, heart failure, ►absence epilepsy, ►neurogenic pain, and ►Parkinson's disease. Most recently, T-type channels are shown to control the vesicular release of neurotransmitters in neurons, and very recent data indicate that they are involved in fast ►catecholamine release in adrenal chromaffin cells.

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Calcium Channels: Regulation of Gene Transcription

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Synonyms

Excitation-transcription coupling; Voltage-gated calcium channels/ligand-gated calcium channels and control of gene expression; Calcium-regulated nuclear signaling

Definition

Nerve activity induces Ca^{2+} influx through voltage-gated calcium channels (►VGCCs), and activates vital functions such as ►neurotransmitter release (NT) and gene transcription. The latter function is often coupled to permanent changes to the structure of synapses (e.g., ►synaptic plasticity) and the survivability of neurons. Recent research indicate that the specificity of local nuclear signaling pathways depends upon the association of specific channel types to cytosolic Ca^{2+}-sensitive factors and not just Ca^{2+} influx *per se*. Indeed, it is only the L-type ($Ca_v1.2$) channels which are critical for the transcriptional regulation of many genes and these contribute only to a fraction of the total Ca^{2+} influx during neural activity. Ca^{2+} influx by other means, such as the ►N-methyl-D-aspartate receptors (NMDA), also contribute to calcium-dependent gene expression changes and share many but not all of the same nuclear signaling pathways.

Characteristics

Calcium as a Signaling Molecule

The nervous system relies on charged molecules to relay information. Whereas the relatively inert Na^+ and K^+ ions serve mostly to establish membrane potential and carry action potentials along excitable membranes, Ca^{2+} has properties that allow it to accomplish additional functions. First, it has a unique affinity for binding ligands containing oxygen-donating groups such as carboxyls, carbonyls, ethers, and alcohols. Second, Ca^{2+} is kept at low levels within the cytosol since it precipitates organic anions and is toxic to cells at high concentrations. These features likely lead to the exploitation of the calcium ion not only as a charge carrier but also as a signaling molecule.

Calcium-regulated Genes

Nerve activity promotes subcellular calcium "hotspots" or microdomains around individual channels, and collectively these active channels contribute to global cellular processes including synaptic plasticity and neuronal survival. An example is long-term memory which involves synaptic connectivity changes activated via ►long term-potentiation (LTP). Strengthening of synapses induced by LTP requires gene transcription mediated by calcium-sensitive signaling pathways [1]. Furthermore, activity-dependent neuronal survival, which is important during cognitive development, also requires calcium-dependent gene transcription [2].

"First responder" genes are termed ►immediate early genes (IEGs), whose transcription is upregulated without a requirement for newly synthesized proteins. The expression of IEGs is tightly regulated in space and time in active neurons by the summation of nerve inputs and local Ca^{2+} flux. ►Brain-Derived Neurotrophic Factor (BDNF) is a classical calcium-activated IEG

that mediates activity-dependent neuronal survival and is required for establishment of LTP (reviewed in [3]). BDNF is a neurotrophin that activates downstream signaling pathways through binding to ►receptor tyrosine kinase TrkB and low affinity receptor p75 (►p75 Neurotrophin Receptor) to exert immediate and long term effects on synaptic activity. Not surprisingly, mutations in the BDNF gene have been correlated with neuronal dysfunction including impaired episodic memory [3]. Numerous other genes encoding transcription factors, growth factors, cytoskeletal proteins, and proteins involved in signaling and metabolism have also been classified as IEGs including *c-fos, fos B, c-jun, jun B, zif268, Egr-3, Cox-2, Rheb, Arc, Narp, β-activin, Homer*, and *nur77*; many have been implicated in aspects of neuronal development and survival, and synaptic plasticity changes [2,4].

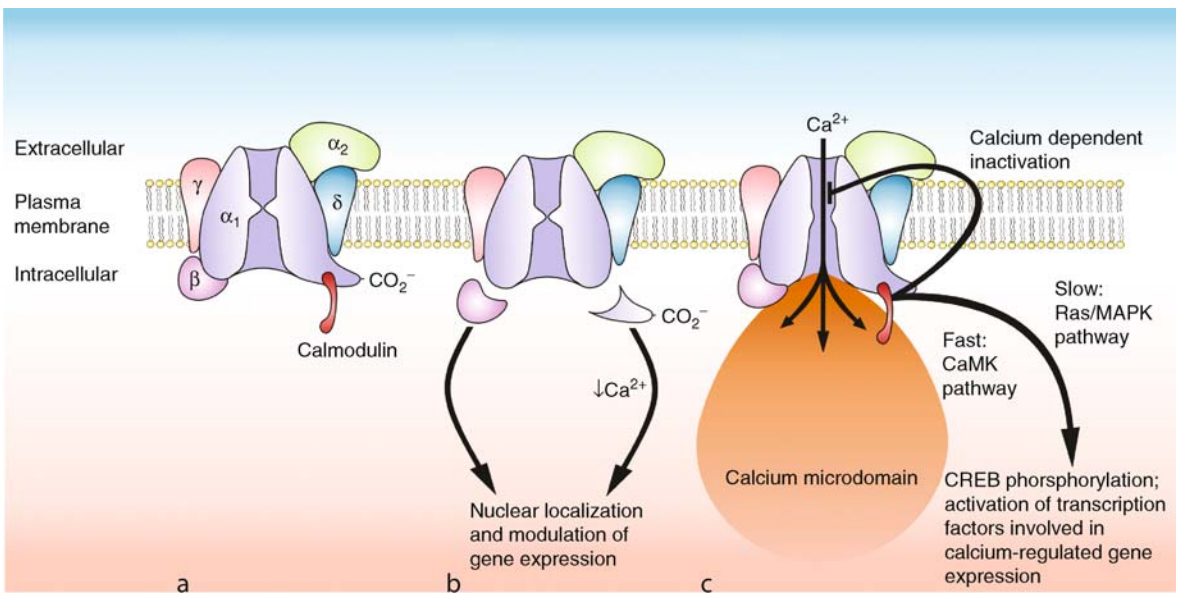
Calcium-mediated Cell Signaling

Calcium signaling depends on a cascade of electrochemical and biochemical events. These include stimulus sensation and opening of a channel or receptor and influx of Ca^{2+} into the cytosol, binding of Ca^{2+} ions to intracellular ligands, and signaling to terminal effectors. Ca^{2+} influx occurs along steep electrochemical gradients across the plasma membrane, through highly-selective channels or receptors including VGCCs and NMDA receptors, or from intracellular stores through ►ryanodine and ►inositol 1, 4, 5-triphosphate receptors (IP_3). Cytosolic Ca^{2+} is quickly buffered and limited to transient microdomains (►Calcium Microdomains) surrounding the pores of open channels (Fig. 1c).

Consequently, calcium-sensing signaling molecules must be in close proximity or directly coupled to channels. Voltage-gated L-type channels, which are important for coupling excitation with transcriptional changes in the nucleus, are localized in the proximal dendrites and cell soma where they are positioned to both sense incoming waves of depolarization originating in the dendrites and to signal to the nucleus.

Calcium-sensitive, Nuclear Signaling Pathways

Calcium/cAMP Response Element Binding protein (►CREB) is a transcription factor whose activity is implicated in calcium-related signaling events and is activated through phosphorylation of a serine residue (Ser-133). Cytosolic Ca^{2+} microdomains trigger CREB phosphorylation via several pathways with distinct temporal kinetics, the most significant of which are the ►Ras/MAPK pathway and the ►calcium/calmodulin-dependent kinasePathway (►CaMK) (reviewed in [3], Fig. 1c). Whereas the CaMK pathway is involved in early phosphorylation of CREB, the Ras/MAPK pathway is required for sustained CREB phosphorylation [5]. Both pathways are critical since a sustained CREB phosphorylation is required for



Calcium Channels: Regulation of Gene Transcription. Figure 1 (a) Illustration of the subunit complex of high voltage-activated calcium channels. Calmodulin or CaM (shown in red) containing EF-hand motifs, bind the C-terminus of the α_1 subunits of calcium channels. (b) Cleaved C-termini of $Ca_v1.2$ channels translocate to the nucleus to activate gene transcription. A β_4 subunit isoform also translocates to the nucleus and interacts with nuclear factors involved in gene expression. (c) L-type channels mediate Ca^{2+} signaling via CaM bound to their C-termini. CaM is activated by Ca^{2+} entry through L-type ($Ca_v1.2$) channels and mediates both calcium-dependent inactivation and gene transcription.

transcriptional activation [5]. Phosphorylated CREB promotes transcription of a variety of IEGs including BDNF and mediates both activity-dependent neuronal survival and synaptic plasticity [3].

Besides CREB, additional calcium-dependent transcription factors have been identified. Like CREB, these are typically regulated by CaM or downstream members of the CaM signaling pathway, and translocate to the nucleus upon activation. These include:

1. ►Nuclear Factor of Activated T cells: NF-AT has been implicated in synaptic plasticity [reviewed in 6]. NF-AT translocates to the nucleus upon dephosphorylation by calcineurin, a protein phosphatase controlled by the CaMK pathway.
2. ►Myocyte Enhancer Factor 2: MEF2 is involved in neuronal survival and apoptosis. Phosphorylation of MEF2 via the Ras/MAPK pathway leads to transcription of MEF2-regulated genes that promote survival of cerebellar granule neurons. During T-cell receptor mediated apoptosis, MEF2 activation via the calcium/CaM pathway leads to the expression of the pro-apoptotic IEG Nur77 [2]. MEF2 can also be cleaved by calcium-activated caspase enzymes, generating pro-apoptotic, dominant-interfering forms that bind DNA to inhibit MEF2 transcription.
3. ►Nuclear factor κB: NF-κB promotes neuronal survival by transcribing genes that inhibit apoptosis such as ►manganese superoxide dismutase (MnSOD), ►Inhibitors of APoptosis (IAPs), and the ►Bcl-2 homologue Bfl-1/A1 [7]. Calcium/CaM mediated dissociation of an inhibitory subunit from the NF-κB hetero-trimeric complex leads to nuclear localization of a transcriptionally active heterodimer [7]. NF-κB has also been implicated in synaptic plasticity changes and spatial learning [7].
4. Downstream Regulatory Element-Antagonist Modulator: ►DREAM contains four EF-hand motifs for binding Ca^{2+}, and acts as a nuclear transcriptional repressor that binds to regulatory DRE motifs of target genes in conditions of low calcium. Genes regulated by DREAM include the IEG *c-fos* and ►Prodynorphin, a transcription factor involved in memory acquisition and pain [8]. Interestingly, in the absence of nuclear Ca^{2+}, DREAM binds CREB and prevents it from recruiting ►CREB Binding Protein (CBP), a factor critical for CREB-mediated transcriptional activation.

L-type calcium channels and control of gene expression

Of the known VGCCs in the nervous system (i.e., Ca_v1 (L-type), Ca_v2 (N-, P/Q-, R-types), and Ca_v3 (T-type)), L-types are the only channel type established to couple excitation with transcription. Selectively blocking L-type channels with ►dihydropyridines inhibits the expression of many IEGs. Intracellular microdomains of Ca^{2+} generated by L-type channels lead to both nuclear signaling and negative feedback regulation of channel gating itself by means of calcium-dependent inactivation. It has been reported that both processes are dependent on the tethering of calcium-sensitive molecules to the channel where they can sense the local increase in calcium concentration. CaM, a cytosolic protein able to directly bind calcium via its EF-hand motifs, remains tethered to L-type ($Ca_v1.2$) channels via an isoleucine-glutamine (IQ) motif in the channel's C-terminus. Disrupting either the ability of CaM to interact with L-type channels or CaM's ability to bind Ca^{2+} leads to loss of calcium-dependent inactivation [9] (Fig. 1c). Subsequent research from Dolmetsch and colleagues illustrates that CaM also mediates nuclear signaling by L-type channels [5] (Fig. 1c). This research group assayed the phosphorylation of CREB and activation of the Ras/MAPK signaling pathway in neurons where endogenous L-type channels had been blocked by dihydropyridines. By transfecting functional drug-resistant L-type channels into cultured primary neurons, Dolmetsch et al. showed that mutating the CaM-binding IQ motif or co-expressing calcium-insensitive CaM abrogated calcium-dependent activation of the Ras/MAPK pathway, CREB phosphorylation, and activation of MEF2. As illustrated in Fig. 1c, this research establishes CaM as a pivotal regulatory center for L-type channels, in channel self-regulation and the feed-forward control of gene expression.

Some intriguing twists in the story of how L-type channels modulate gene transcription are now emerging. The C-terminus of $Ca_v1.2$ translocates to the nucleus as a ~75 kDa peptide (termed CCAT) after proteolytic cleavage at the cell membrane. In the nucleus, CCAT peptide binds transcriptional regulator ►p54(nrb)/NonO, associates with endogenous promoters, and promotes a significant up-regulation of 16 genes (e.g., axon guidance factor ►Netrin4 and gap junction protein Cx31.1) and down-regulation of 31 genes (e.g., ►NMDA receptor subunit Grin2dand the ►Na^+/Ca^{2+} exchangerScl8A1) [10] (Fig. 1b). Nuclear translocation of CCAT is observed in several central neuron types, especially in adults and heterologous expression of CCAT promotes increased neurite outgrowth in cultured primary neurons. Interestingly, CCAT translocation requires low cytosolic Ca^{2+} levels suggesting a mode of transcriptional regulation unlike the CaM dependent pathway which requires Ca^{2+} and neuronal activity. It has been suggested that a CCAT-like cleavage mechanism may be widely applicable since the C-terminus of the P/Q-type channel ($Ca_v2.1$) is also cleaved and translocates to the nucleus; yet, it remains to be determined whether truncated $Ca_v2.1$ peptides affect gene expression.

With the exception of T-type channels, the pore-forming α_1 subunits of VGCCs associate with accessory

subunits (termed α_2, δ, β, and γ) which significantly modulate the electrophysiological properties and surface expression of the α_1 subunits (Fig. 1a). Recent evidence suggests that a short β_4 isoform translocates to the nucleus and interacts with heterochromatin protein 1γ to promote gene silencing, however the underlying mechanisms and significance remains to be elucidated (Fig. 1b).

Control of Gene Expression by NMDA, Ryanodine, and IP_3 Receptors

Calcium flux through post-synaptic NMDA receptors shares many of the downstream targets as L-type calcium channels to promote gene expression and neuronal survival. The similarities with L-type channels include activating CREB by phosphorylation, promoting the expression of some IEGs [8], and nuclear signaling via the CaMK and the Ras/MAPK signaling pathways. It has been reported that different calcium sources may be required for different phases of gene transcriptional activation. In particular, the NMDA receptors mediate an earlier phase of CREB phosphorylation (i.e., 10 min after depolarization), while the L-type channels are required in later stages. NMDA receptors also operate through downstream effectors associated with LTP induction, that do not overlap with L-type calcium channels. For example, ►EphB receptor tyrosine kinases localize at excitatory synapses and enhance the expression of NMDA receptor-mediated genes, but not those mediated by L-type channels. Interestingly, variations in the composition or location of the NMDA receptors create highly divergent signaling. Whereas synaptic NMDA receptors mediate neuronal survival, calcium entry via extra-synaptic receptors inhibits CREB phosphorylation and promotes cell death. Furthermore, changes in the composition of NMDA receptor subunit alters MAPK pathway signaling leading to either LTP or LTD (►Long Term Potentiation and Long Term Depression).

Internal calcium sources may also participate in regulating gene transcription, but there is not much evidence for this mechanism occurring in neurons. IP_3 receptor activity can mediate the phosphorylation of CREB and activate NF-AT and NF-κB transcription factors in both muscle and neuronal cells (reviewed in [6]). ►Ryanodine receptor-mediated Ca^{2+} influx has been linked to activation of the transcription factor NF-AT and expression of the slow myosin heavy chain I gene in muscle (reviewed in [6]).

Conclusion

Gene transcriptional changes are the capacity of neurons to adapt to changing conditions, such as to modify their structure, their survivability and enhancement of connectivity. Regulation of gene expression is necessary in neural development, for the process of learning and memory, and for apoptosis. Importantly, regulatory mechanisms may be harnessed for possible treatment of neurodegenerative disease.

Specificity in gene regulation is governed by nerve activity and calcium flux. Different calcium sources mediated through L-type calcium channels as well as NMDA receptors and intracellular sources converge through multiple, and often overlapping, signaling pathways (e.g., CREB, CaMK, Ras/MAPK and cAMP dependent protein kinase A (reviewed in [3,6])). These likely contribute collectively to global cellular changes in nuclear Ca^{2+} to enhance the transcription of IEGs. At a local level, calcium is sensed by tethered CaM at the C-terminus of L-type calcium channels. CaM serves as a regulatory control point for tuning up or down calcium channel activity and its downstream regulators of gene transcription. Interestingly, low calcium also appears to be a signal for gene expression, as both the transcriptional modulator DREAM as well as the C-terminal cleavage product CCAT of L-type channels, require low nuclear and cytosolic Ca^{2+} levels respectively for activation [8,10]. Future experimentation will further clarify how the varied signaling mechanisms activated by calcium, coming through calcium channels or other sources (eg. NMDA receptors), contribute to the regulation of gene transcription.

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Calcium Chelator

Definition

Calcium ions have a double positive charge. Calcium chelators are molecules that bind calcium and cover the ion in a way that it is no longer available for cellular metabolism. It was the invention of calcium chelators that allowed understanding the role of calcium in biological cells, because calcium concentrations in cells are so low that it is impossible to create artificial solutions with lower calcium concentrations unless calcium is removed using chelators. The event of calcium chelators, that can be titrated to create known calcium concentrations, made this ion accessible to direct experimental analysis.

Calcium-regulated Nuclear Signaling

►Calcium Channels: Regulation of Gene Transcription

Calibration

Definition

A routine undertaken to correlate the readings of an instrument with known physical quantities. This is often carried out by applying a series of carefully controlled physical quantities, recording the instrument readings and plotting a graph of the instrument readings as a function of the physical quantity.

►Measurement Techniques (Pressure)

Calmodulin

Definition

Calmodulin (CaM) is a ubiquitious, calcium-binding protein that can bind to and regulate a multitude of different protein targets, thereby affecting many different cellular functions. For example, it binds to RyRI, the sarcoplasmic reticulum Ca^{2+} release channel in skeletal muscle, and partially activates the channel at low Ca^{2+} concentrations but acts as an inhibitor of Ca^{2+} release at high Ca^{2+} concentrations.

►Excitation-Contraction Coupling

Caloric Stimulation

Definition

Caloric stimulation of the labyrinths is a procedure for stimulating the vestibular labyrinths without moving the head, and is most often used in a clinical evaluation of the vestibular system. The principal advantage of caloric stimulation is that one labyrinth can be tested at a time, whereas natural or artificial head movements stimulate both labyrinths and sometimes the otolithic organs too. This stimulation induces nystagmus via vestibulo-ocular reflex (VOR) pathways, which in a healthy person, builds up slowly, reaches slow-phase angular velocities up to 80°/s (ice water irrigation), and then decays slowly.

Actual stimulation is produced by circulating warm (up to 40°C) or cool (down to 0°C) water in the outer ear canal either directly or by use of a small balloon that fits snugly in the canal. The effects of this stimulation are produced mainly by temperature gradients in the horizontal (lateral) semicircular canal, which is closest to the outer ear canal, although minor direct effects on firing rates of primary vestibular afferents and stimulation of other semicircular canals may also occur.

►Brainstem Burst Generator
►Nystagmus
►Peripheral Vestibular Apparatus
►Vestibular Tests: Caloric Test
►Vestibulo-ocular Reflexes (VOR)

Calsequestrin (CSQ)

Definition

The major lumenal sarcoplasmic reticulum Ca^{2+} binding protein located in the junctional terminal cisternae that binds Ca^{2+} with high capacity but low affinity which enables it to bind and release large quantities of Ca^{2+} rapidly.

►Excitation-Contraction Coupling

Calyx of Held Synapse

Definition

A large glutamatergic synapse in the mammalian auditory brainstem between a projection of globular bushy cells (presynaptic) in the anterior ventral cochlear nucleus and the cell soma of a principal neuron (postsynaptic) in the medial nucleus of the trapezoid body (MNTB).

►Bushy Cells
►Cochlear Nucleus
►Synaptic Transmission: Model Systems
►Trapezoid Body

Camera Calibration

Definition

A procedure by which parameters defining camera positions, orientations, and lens distortions are determined in image-based motion analysis.

►Motion Analysis

CaMKII (CaM Kinase II)

►Calcium Binding Proteins

►Calcium/Calmodulin-Dependent Protein Kinase ll in Neurons

cAMP

Definition

►Cyclic AMP

cAMP-dependent Protein Kinase (Protein Kinase A)

Definition

A family of protein kinases whose activity are dependent on the level of cAMP in the cell.

cAMP/PKA-mediated Up-regulation

Definition

Sequence of events that originate from a Gs protein-mediated activation of adenylate cyclase (AC). The activated AC raises the intracellular cAMP levels and promotes the activation of protein kinase A, which phosphorylates specific intracellular Ca^{2+} channel sites (phosphorylation sites). In the case of the cardiac Cav1.2 channel, the phosphorylated channel increases the probability of opening and causes increased Ca^{2+} flux into the cell.

►Calcium Channels – an Overview

cAMP Response Element (CRE)

Definition

cAMP response element is a leucine zipper domain in DNA which is bound by CREB transcription factors, resulting in the modulation of gene transcription.

CAN

Definition

Ca^{2+}-activated nonspecific cation channel.

►Respiratory Pacemakers

Canal Neuromast

Definition

Neuromasts found within canals, primarily in phylogenetically conservative locations on the head and trunk. Typically acceleration sensitive.

►Evolution of Mechanosensory and Electrosensory Lateral Line Systems

Canal Plugging

Definition

Occlusion of the semicircular canals to block sensitivity to angular motion stimuli to study the influence of individual canal afferent inputs to the vestibular reflex system. Spontaneous discharge of primary afferent inputs to the brainstem and residual angular motion sensitivity persist even after complete surgical occlusion of the canal. The magnitude of the plugged canal response increases with angular acceleration and is largest for rapid or high frequency head movements.

►Semicircular Canals
►Vestibulo-spinal Reflexes

Canalo-ocular Test at Medium Frequency

►Vestibular Tests Head-Shaking Test

Cancer

Definition

Class of diseases or disorders characterized by uncontrolled division of cells and the ability of these cells to invade other tissues, either by direct growth into adjacent tissue through invasion or by implantation into distant sites by metastasis.

Cancer-associated Retinopathy

Definition

►Inherited Retinal Degenerations

Candelabrum Cell

Definition

Candelabrum cells are inhibitory interneurons in the cerebellar cortex. Their cell bodies are in the Purkinje cell layer and their dendrites reach into the molecular layer. Candelabrum cell axons also reach into the molecular layer.

Cannabinoids

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Definition

►Cannabinoids are chemicals that bind to ►cannabinoid receptors. These lipophilic compounds are commonly classified by their source: herbal (derived from the plant *Cannabis sativa*), endogenous (produced in animal cells) or synthetic, and by their chemical structures (e.g., classical, non-classical, aminoalkylindole).

Characteristics

Cannabis sativa, also known as marijuana, has been used for over 4,000 years as a recreational and therapeutic drug. Cannabis use produces a range of physiological and psychoactive effects such as CNS depression, appetite stimulation, memory deficits and analgesia. Activity of the ►endocannabinoid system is broadly involved in motor coordination, ►memory, ►learning and ►cognition, ►nociception, appetite and emesis, ►reward, psychological effects of ►anxiety reduction, sensory perception, ►mood enhancement and mild sedation, anti-►inflammation, anti-►excitotoxicity, ►neuroprotection and ►neurogenesis.

The isolation of the ►psychoactive constituent of cannabis – ►delta-9-tetrahydrocannabinol (THC), generation of synthetic cannabinoid compounds, discovery of ►endocannabinoids and cloning of cannabinoid receptors have facilitated great progress in understanding the mechanisms by which cannabinoids elicit their effects. Such advances have revealed that dysfunction of the endocannabinoid system is involved in the pathogenesis of a variety of diseases and reinforced that cannabinoid compounds may be of therapeutic benefit in these and other disorders.

Cannabinoid Receptors

The majority of the biological effects of cannabinoids are mediated through two class A (►rhodopsin-like) ►G-protein coupled receptors (GPCRs) termed cannabinoid receptor 1 (CB1) and 2 (CB2). Although THC and

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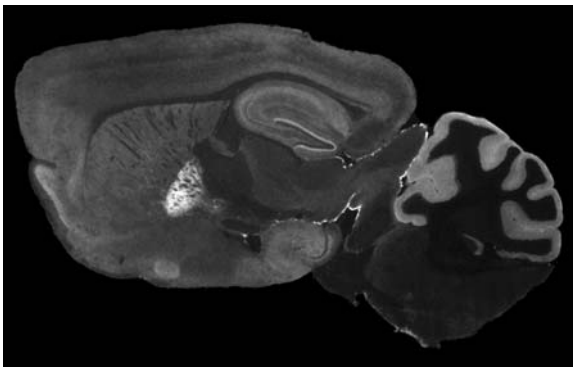
a number of other cannabinoids have similar affinities for these receptors, their amino acid sequences share only 44% identity and their distributions in the body and ►brain are very different. Not surprisingly therefore, the receptors are responsible for different functions.

CB1 is expressed in peripheral tissues including the lungs, liver, kidneys and reproductive organs, and is extremely abundant in the mammalian ►CNS. Distribution is widespread with particularly high levels present in the ►basal ganglia, ►hippocampus, ►cerebellum and ►cortex (Fig. 1); areas which correlate well with the effects of cannabinoids on memory, perception and movement control. Consistent with the lack of lethality of cannabis administration, CB1 is essentially absent from regions of the brainstem controlling cardiovascular and respiratory functions [1]. Splice variants of CB1 have been reported, however their physiological relevance is not yet established.

As is the case for all GPCRs, CB1 receptor activation is transduced into intracellular signals via interaction with a ►G-protein complex consisting of alpha, beta and gamma subunits. Association of CB1 with the inhibitory G-alpha i/o family is most commonly observed, although affinity for Gs has also been demonstrated under particular conditions. Activation of Gi/o inhibits ►adenylate cyclase and the accumulation of ►cyclic AMP (cAMP), with downstream effects including the activation of ►inward rectifying K^+ channels and the regulation of cAMP-dependent enzymes. Other consequences of CB1 activation, likely mediated by the G-protein beta-gamma subunits, include the inhibition of calcium channels and the induction of ►immediate early gene expression. In the brain, CB1 signaling is associated with the modulation of neuronal excitability. Depolarization-induced release of endocannabinoids into synaptic terminals and subsequent activation of pre-synaptic CB1 receptors tends to inhibit the release of other ►neurotransmitters, including ►glutamate and ►acetylcholine. This activity, combined with CB1's wide distribution, contributes to explaining how cannabinoids influence such a wide variety of brain functions that are primarily controlled by different neurotransmitter-receptor classes. Further, dimerization of CB1 with other receptors, such as ►dopamine D2 and ►orexin receptors, has been demonstrated and the resultant alteration of receptor activity represents a further level of complexity in this system.



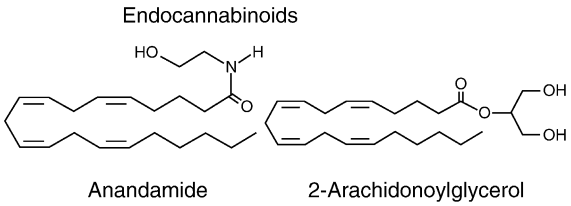
Cannabinoids. Figure 1 Immunohistochemical localisation of the CBI receptor in the mouse brain.

CB2 receptor expression was until recently considered to be limited exclusively to the periphery, with the highest levels observed in immune and haematopoietic cells. However it is now established that CB2 is expressed in ►microglia, an immune cell found in the brain, and in selected ►neurons of the ►brainstem. During neurodegeneration and following brain injury, microglia tend to proliferate and become active, upregulating CB2 expression and often producing inflammatory damage additional to the primary insult. CB2 stimulation tends to reduce microglial reactivity, therefore this system may represent an attractive therapeutic target. CB2 signaling is primarily mediated by interaction with Gi/o, but differs from CB1 in that activation does not appear to affect calcium and potassium ion channels.

Although CB1 and CB2 receptors are considered to be the primary mediators of cannabinoid effects, pharmacological evidence suggests that still unidentified cannabinoid receptors might exist, for example in the hippocampus, modulating the release of ►glutamate, and on ►endothelial cells. Signaling in response to some cannabinoids is observed in the brains of CB1/CB2 knockout mice which is suggestive of additional sites of action. Initial characterization of a cannabinoid receptor candidate known as GPR55 demonstrated its sensitivity to some cannabinoids, its presence in several CNS cell types and that its activation increased intracellular calcium. Interestingly, some cannabinoids are able to bind to and activate the transient receptor potential vanilloid type 1 (►TRPV1) receptor, an interaction which may be involved in nociception. Cannabinoids have also been noted to possess anti-oxidative and neuroprotective properties which do not appear to be receptor mediated, however high cannabinoid concentrations are required and it is thus unclear as to whether this effect is physiologically relevant or holds therapeutic potential. Further research to characterize and classify these potential interactions is warranted [2].

Endogenous Cannabinoids

Several ►endogenous cannabinoid ligands (endocannabinoids) have been isolated and demonstrated to bind to cannabinoid receptors. These compounds are all derived from ►arachidonic acid. To date the most studied of these are ►anandamide and ►2-arachidonoyl glycerol (Fig. 2). 2-arachidonoyl glycerol exhibits higher selectivity and



Cannabinoids. Figure 2 Structures of the endocannabinoids.

efficacy for CB1 and CB2 receptors than anandamide, which also interacts with non-cannabinoid receptor targets (e.g., ►TRPV1). The endocannabinoids are synthesized "on demand" in response to increased intracellular calcium, and released from cells immediately following their production. Recent studies have identified synthesizing and degradative enzymes for both of these compounds, and these enzymes provide new drug targets for the manipulation of endocannabinoid levels in vivo [3].

Cannabinoid Based Drug Therapies: Now and in the Future

Cannabinoids have been implicated in many neurological diseases and conditions that originate in or are mediated by the CNS. Those where aberrations in the endocannabinoid system have been linked to disease mechanisms and pathology include neuropsychiatric diseases such as Tourette's syndrome, ►bipolar affective disorder and ►schizophrenia, and neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS; ►Lou Gehrig's disease), ►multiple sclerosis (MS) and ►Alzheimer's, ►Parkinson's, and ►Huntington's diseases. Additionally, cannabinoids are postulated as symptomatic therapeutics for conditions including ►stroke, ►epilepsy, glaucoma, obesity and ►addiction.

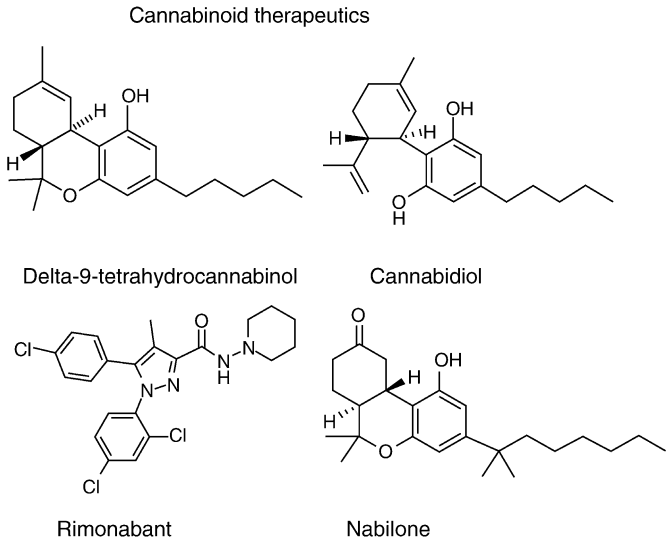
Few cannabinoid compounds are currently approved for pharmaceutical use (Fig. 3). Synthetic THC is available for prescription in capsule form as dronabinol (marketed as Marinol®) and an analog nabilone (marketed as Cesamet®). These products were originally approved for the suppression of nausea in cancer sufferers and were later approved as appetite stimulants for use by patients with HIV and cancer, who commonly experience a wasting syndrome. Subsequent approval has been granted for treatment of MS ►neuropathic pain. An aerosol form of dronabinol is under investigation for migraine treatment in addition to the existing indications (http://www.marinol.com, http://www.cesamet.net).

Sativex® is a prescription drug administered as an oromucosal spray produced primarily from the *Cannabis* plant extracts THC and cannabidiol. Sativex® was approved in 2005 in Canada for the symptomatic relief of neuropathic pain in MS with many current clinical studies investigating its potential use for the control of spasticity and in several other pain conditions (http://www.gwpharm.com). The most recently approved pharmaceutical cannabinoid compound is the CB1 inverse agonist Rimonabant (Acomplia®). Available since 2006 in some European countries for prescription as an anorectic anti-obesity drug, it is indicated for use in conjunction with diet and exercise in obese patients. Rimonabant has also been proposed to assist with smoking cessation and to aid in the prevention of weight gain in former smokers; however approval is yet to be granted for these indications (http://en.sanofi-aventis.com).

Early clinical trials have been undertaken to assess a THC metabolite-like synthetic cannabinoid, IP 751 (Ajulemic Acid/CT-3), as an anti-inflammatory/►analgesic medication (http://www.indevus.com). Further clinical trials of cannabinoid drugs are expected in the near future including: inhibitors of endocannabinoid enzymatic breakdown (►fatty acid amide hydrolase inhibitors) such as URB597 (also known as KDS-4103) for the treatment of anxiety, depression and pain; compounds such as oleoylethanolamide (KDS-5000) that activate endocannabinoid related pathways through mechanisms other than CB1 or CB2 for the control of appetite, obesity and liver disease; compounds that activate central and/or peripheral cannabinoid receptors for neuropathic pain (topical anandamide to target receptors in peripheral sensory nerves, KDS-2000 http://www.kadmuspharma.com) and nociceptive pain management (CB2 selective agonists, Cannabinor http://www.pharmoscorp.com). Recent research has demonstrated that the cannabinoid quinone HU-331 is a highly specific inhibitor of topoisomerase II and therefore shows potential as an anticancer drug [4].

Molecular and preclinical studies have demonstrated that cannabinoid drugs could also be useful in other specific conditions. For example, in models of the heritable neurodegenerative illness Huntington's disease, various cannabinoid compounds have decreased toxin-induced striatal degeneration in rats and protected cells expressing the pathogenic protein from cell death. CB1 receptors are lost early in the disease and preferentially to colocalized receptors, suggesting involvement of the cannabinoid system in disease mechanisms [5]. Several cannabinoid-related treatments decrease motor deficits in animal models of the degenerative movement disorder Parkinson's disease, potentially providing protection against neuronal injury and influencing local pathological inflammatory events [6].

Hyperactivity of the endocannabinoid system is postulated to be involved in schizophrenia pathology or the mechanisms of negative disease symptoms.



Cannabinoids. Figure 3 Cannabinoid compounds currently approved for therapeutic use.

Alterations in the central endocannabinoid system in people with schizophrenia include increased density of CB1 in subregions of the ►prefrontal cortex and increased anandamide in the ►cerebrospinal fluid. There is also some suggestion that cannabis consumption may induce ►psychosis and schizophrenia in susceptible people [7].

Pathogenic mechanisms underlying ►motorneuron degeneration in ALS are unclear. However, endocannabinoids are involved in the modulation of several proposed mechanisms including excitotoxicity, oxidative stress, neuroinflammation and microglial activation, which may explain the neuroprotective effects of increasing endocannabinoid levels in models of ALS. Disease progression in mouse models has also been delayed with CB1 and CB2 receptor agonists [5].

While the endocannabinoid system does not appear to contribute to the cause of stroke, neuroprotective endocannabinoid signaling in response to brain injury has been observed. In animal models both CB1 and CB2 receptor expression in the brain is increased, anandamide levels are elevated and CB1 blockade is protective [8]. Finally, the endocannabinoid system has been implicated in seizure activity and epilepsy due to its ability to modulate the release of other neurotransmitters and reduce excitotoxicity; properties which may help to explain cannabinoid anticonvulsant properties. As endocannabinoids are synthesized "on demand" seizure activity can directly stimulate increased production. However, cannabinoids have also been suggested to have proconvulsant activity in certain circumstances, therefore further investigation will be necessary before cannabinoids can be pursued in a therapeutic capacity [9].

There is a wealth of research currently being carried out in the cannabinoid field. This will no doubt lead to the emergence of many novel drug targets for neurological disease over the coming years.

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Capacitance (Electrical)

Definition

Ability of a capacitor to separate and store electrical charges, measured in farads (F).

►Action Potential
►Action Potential Propagation
►Cable Theory
►Membrane Potential: Basics

Capacitance Measurement

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Definition

The process of measuring the time course of changes in membrane capacitance. In this essay, we restrict our attention to patch-clamp capacitance measurements used to quantify changes in membrane surface area that accompany ►exocytosis and ►endocytosis.

Characteristics

Purpose

Molecules that mediate cell-to-cell communication, such as hormones and neurotransmitters, are packaged and stored within cells in membrane-delimited vesicles. In neurons and other excitable cells, the trigger for release of these signaling molecules is influx of Ca^{2+} through voltage-gated Ca^{2+} channels upon membrane depolarization. The consequent elevation of the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) triggers the fusion of vesicles with the cell plasma membrane, and release of the vesicle contents to the extracellular space by the process of exocytosis. The vesicle membrane is taken up again into the cell by the process of endocytosis. Application of membrane capacitance measurements, in conjunction with other techniques, has greatly increased our understanding how Ca^{2+}triggers exocytosis and how specific proteins and second-messenger cascades regulate exocytosis and endocytosis.

The capacitance of the cell membrane is proportional to its area, thus the insertion of vesicle membrane during exocytosis results in an increase in capacitance, whereas endocytosis decreases membrane capacitance. Just as patch-clamp techniques can resolve the currents due to the opening and closing of individual ion channel molecules, capacitance measurements from small membrane patches can resolve the fusion (exocytosis) and fission (endocytosis) of individual synaptic vesicles with millisecond time resolution [1].

The modern era of membrane capacitance measurements dates to the early days of the patch-clamp recordings. In a seminal report in 1982, Neher and Marty described changes in membrane capacitance associated with exocytosis in chromaffin cells [2]. Unlike single-channel recording, however, capacitance measurement was slow to catch on as a mainstream approach and only a handful of laboratories used the technique in the 1980s. Capacitance measurements blossomed in the 1990s, partly due to the emergence of powerful software that greatly simplified application of the method. The capacitance technique continues to make a large contribution towards a mechanistic understanding of exocytosis and endocytosis.

Advantages and Disadvantages

Chief Strengths of the Capacitance Technique

1. Under appropriate conditions, the time course of fusion of individual vesicles, including the formation of the ►fusion pore, can be resolved. The fusion reaction has been shown to be reversible, in that a step increase in capacitance is followed by a decrease in capacitance of the same size (e.g. [3]). This allows one to follow the duration of time that vesicles remain fused with the plasma membrane. A particularly powerful approach for correlating single-vesicle fusion kinetics with the discharge of vesicle contents is ►patch-amperometry [3].
2. The process of membrane fusion can be monitored independently from the discharge of vesicle contents. ►Carbon-fiber amperometry (reviewed in [4]) and styryl dye (e.g. FM143) fluorescent measurements are powerful techniques for measuring the efflux of material from vesicles during exocytosis. However, capacitance measurements uniquely identify the distinct kinetics of vesicle membrane fusion and fission. Understanding the kinetics of membrane fusion is essential to develop quantitative models relating $[Ca^{2+}]_i$ to exocytosis.
3. Patch clamp capacitance measurements allow a high level of control over parameters that trigger and modulate exocytosis:

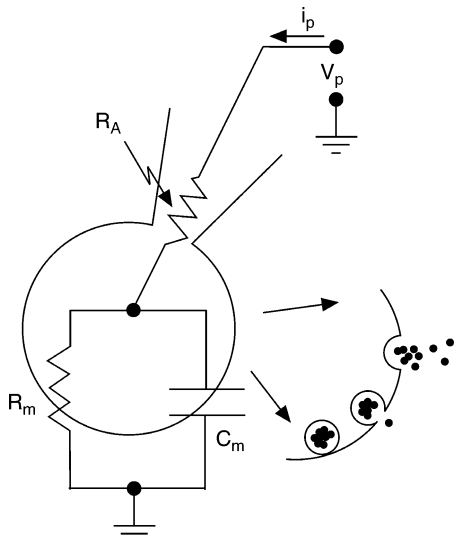
- Patch-clamp capacitance measurements occur under voltage-clamp control. This allows the experimenter to depolarize the cell in a controlled manner, and measure the relationship between Ca^{2+} influx through voltage-gated Ca^{2+} channels and exocytosis assayed with the capacitance technique. It is thus possible to determine which steps in the stimulus-secretion cascade, (membrane depolarization leading to Ca^{2+}

influx leading to Ca^{2+}-triggered exocytosis) are affected by an experimental maneuver such as application of a drug.

- Substances such as fluorescent indicators, drugs, peptides and soluble second messengers can easily be loaded into a cell by diffusion from the pipette solution during whole-cell recording. For example, Ca^{2+} bound to a high-affinity photo-labile chelator ("cage") can be introduced into the cell. Photolysis of the cage with ultraviolet light can be used to elevate $[Ca^{2+}]_i$ uniformly throughout the cell, while the time course of exocytosis is measured using the capacitance technique (e.g. [5]). This approach is the most direct way currently employed to measure the relationship between $[Ca^{2+}]_i$ and exocytosis.

Chief Weaknesses of the Technique

1. The greatest weakness of the capacitance technique is that it only reports the difference between the rates of exocytosis (addition of surface membrane) and endocytosis (removal of surface membrane). This is not a large issue in recordings from membrane patches, where step changes in capacitance due to fusion or fission of single vesicle can be resolved. In contrast, in whole-cell or perforated-patch recordings, unitary events cannot be resolved and increases in capacitance may underestimate the rate of exocytosis if endocytosis is occurring at the same time. In the whole-cell recording condition, application of a mild stimulus often results in a rapid increase in capacitance followed with a much slower "compensatory" decrease towards the baseline value. Under this experimental condition, the separation of exocytosis and endocytosis is relatively clear because exocytosis is much faster than endocytosis, and the initial capacitance increase is interpreted as reflecting exocytosis. On the other hand, endocytosis is more rapid when the stimulus elevates $[Ca^{2+}]_i$ to many 10s of μM, or when the cellular contents are better preserved such as during perforated-patch recording [6]. Under these conditions, great caution must be applied in quantitatively relating capacitance changes to exocytosis and endocytosis. Carbon-fiber amperometry can be used to confirm the relationship between capacitance increases and exocytosis.
2. Capacitance changes may result from phenomenon other than changes in membrane surface area. The capacitance of a biological membrane is usually assumed to be ~10 $fF/\mu m^2$, but this value will change slightly depending on the mobility of charges in integral membrane proteins such as voltage-gated ion channels. For example, Horrigan and Bookman [7] have described a transient change in capacitance following depolarizing steps that is unrelated to exocytosis or endocytosis, but instead reflects recovery of Na^+ channels from inactivation. This non-exocytosis-related capacitance change is reproducible and transient, and thus can be eliminated from the capacitance trace by subtraction. In addition, large changes in membrane resistance can cause erroneous changes in estimated capacitance unless great care is taken.
3. The usual application of the capacitance technique is based on a simple, 3-component equivalent circuit representation depicted in, and thus can only be applied to preparations with a single ►membrane compartment. The technique has been most widely applied to endocrine cells because these spheroidal cells are well described by the equivalent circuit of Fig. 1. Special neural cells such as cochlear hair cells and retinal bipolar nerve terminals [8] are also amenable to the technique. Capacitance measurements have recently been made in presynaptic terminals at the calyx of Held [9] and in hippocampal mossy fiber terminals [10]. These preparations are not always well described by a single ►membrane compartment model, however, simulations indicate that the estimated capacitance change faithfully follows changes in the terminal capacitance [9,10]. The extension of the capacitance technique to explicitly account for more complex equivalent



Capacitance Measurement. Figure 1 The equivalent circuit commonly used as a basis for capacitance measurements during patch-clamp recordings. The whole-cell patch clamp configuration is illustrated, but the same equivalent circuit, with different parameter values, applies to on-cell recordings from membrane patches. The inset depicts the increase in membrane surface area, and thus C_m, that occurs during exocytosis. R_A is the "access" resistance through the patch-clamp pipette, whereas R_m and C_m are the membrane resistance and capacitance, respectively.

circuits than represented in Fig. 1, is likely to be an important future direction for increasing the applicability of this powerful technology.

Principles

Present here is only a very brief survey of techniques for estimating changes in membrane capacitance related to exocytosis and endocytosis, see [11] for a detailed treatment. Most capacitance techniques are based on the three component equivalent circuit of the recording configuration depicted in Fig. 1. In this circuit, we neglect the pipette capacitance because the current passing through this pathway is electronically subtracted upon proper adjustment of the pipette capacitance compensation circuitry of the patch-clamp amplifier. During whole-cell recording of a neuroendocrine cell, typical parameters are $C_m \sim 6$ pF, $R_A \sim 8$ MΩ, and $R_m > 2$ GΩ. For on-cell recording, R_A is somewhat smaller and C_m is a fraction of a pF.

The most common approach to estimating capacitance changes is to apply a sinusoidal voltage stimulus and analyze the resulting sinusoidal current. The amplitude of the stimulus sinusoid is usually less than 50 mV, whereas the frequency ranges from ~ 1 kHz for whole-cell recordings to 50 kHz or higher for on-cell measurements. A significant limitation is that a single sinusoid only provides two pieces of information (magnitude and phase), whereas there are three unknown components of the equivalent circuit. Next are described two approaches used to obtain the additional information needed.

In the ►"sine + dc" approach, the dc (average) current is measured and used, together with an estimate of the extrapolated zero-current potential, to estimate the dc conductance ($R_A + R_m$) [12]. This approach is incorporated in "Pulse" and "PatchMaster" (HEKA Inc., Lambrecht, Germany) software, and is probably the most widely used approach currently for capacitance measurements in the whole-cell configuration. The simplest version of the sine + dc approach assumes the reversal potential does not change during the recording. The sensitivity of capacitance estimates to errors in the value of the assumed reversal potential is small if R_m is high (GΩ range). More complicated multi-sinusoid or square-wave approaches are necessary if the R_m is both small and changing.

The ►piecewise-linear approach is the original implementation of the patch-clamp capacitance technique by Neher and Marty [2]. A single-frequency sinusoid voltage stimulus is applied and a phase-sensitive detector (lock-in amplifier) is connected to the patch-clamp amplifier, to extract the component of the sinusoidal current that is proportional to changes in membrane capacitance. Thus, the output signal of the lock-in amplifier, when set to an appropriate phase, is directly proportional to changes in membrane capacitance but has little sensitivity to changes in R_A or R_m. Dithering of the membrane capacitance compensation knob of the patch-clamp amplifier is used both to find the appropriate phase setting of the lock-in amplifier and to calibrate the capacitance signal. A subsequent variant of the technique ("phase tracking") uses computer-controlled dithering of series resistance introduced between the bath and ground to find the appropriate phase setting [13]. The piecewise-linear approach was initially quite popular because it can be implemented entirely in hardware (e.g. in the Cairn Optopatch patch-clamp amplifier), however, it has largely been replaced by more powerful (and less *ad hoc*) computational approaches for whole-cell capacitance measurements.

A number of ►multi-sinusoid approaches are also used. In the case of two sinusoids there are 4 pieces of information to determine the values of the three unknown parameters. Optimal use of the information to "fit," i.e. estimate the parameters with the minimal variance "noise," is a complex problem that is thoroughly addressed in an elegant study by Barnett and Misler [14]. A number of sub-optimal, but computationally simpler, *ad hoc* approaches to estimate the equivalent circuit parameters from dual sinusoid excitation have also been implemented. A challenging problem with all multi-sinusoid approaches is optimizing the choice of amplitudes and frequencies of the stimuli, and therefore these approaches tend to give noisier estimates of membrane capacitance than single-sinusoid techniques. In addition, the non-ideal frequency dependence of C_m results in an underestimation of R_m (unpublished observations).

Approaches using ►square-wave stimuli are also used. In response to a square step in pipette potential, the equivalent circuit depicted in Fig. 1 will respond with a transient current that decays with an exponential time course.

Fit of the current transient to an exponential function can be used to produce estimates of the three circuit parameters. An excellent implementation of this approach is described in [15]. This approach can be quite robust in that estimates of C_m can be generated that are quite insensitive to changes in R_A and R_m, and C_m estimates can be produced with nearly as low a noise as sinusoidal techniques [15]. This method requires a high bandwidth setting of the patch-clamp amplifier, a high sampling rate and is computationally intense. Nevertheless, an efficient algorithm running on a modern computer can generate estimates at ~100 Hz [15].

Conclusion

Any of the above techniques, when carefully applied, can produce valid estimates of changes in membrane

capacitance related to exocytosis and endocytosis, so the choice of technique often depends on finding an attractive software package. In general, for capacitance techniques to be truly useful, they must be embedded within a powerful, flexible software package that is capable of executing complex stimulus protocols while recording and displaying multiple data streams in real time.

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Capacitative Ca^{2+} Entry

Definition

The phenomenon of capacitative Ca^{2+} entry has been identified upon the receptor-mediated or pharmacologically induced depletion of intracellular endoplasmic Ca^{2+} stores. In response to depletion of the intracellular Ca^{2+} stores, stimulation of a plasma membrane Ca^{2+} entry mechanism can be measured, being interpreted as a refilling mechanism in order to restore the Ca^{2+} loading of the endoplasmic reticulum. In this context, a distinct Ca^{2+} release-activated Ca^{2+} current has been identified and described as Icrac.

Capacitative Current

Definition

►Action Potential

►Action Potential Propagation
►Cable Theory
►Membrane Potential: Basics

Car Sickness

►Anti-Motion Sickness Drugs

Carbon Monoxide Poisoning

Definition

Carbon monoxide poisoning is due to the extremely high affinity of carbon monoxide to hemoglobin and ►myoglobin, where it replaces oxygen depending on its concentration, resulting in hypoxia, anaerobic metabolism and lactic acidosis. Clinical symptoms include shortness of breath, headache, confusion, emotional lability, nausea, vomiting, diarrhea, clumsiness, ►syncope and, in severe cases, cerebral and pulmonary edema, respiratory depression and ►coma.

Cardiac Arrhythmias

Definition

An abnormal heart rhythm that may be too slow (bradycardia), too rapid (tachycardia), irregular, or too early.

Cardiac Ganglia

Definition

Cardiac ganglia are autonomic ganglia that lie close to the surface of the heart, around the origins of the great vessels.

►Autonomic Ganglia

Cardiac Output

Definition

Cardiac output refers to the volume of blood ejected by the left ventricle, and is usually expressed in milliliters per minute. Cardiac output is therefore the mathematical product of heart rate (contractions per minute) and stroke volume (ml of blood ejected per contraction). In a resting human adult, this may amount to approximately 5,000 ml/min but can range from as little as 2,000–3,000 ml per minute up to 25,000 ml per minute depending upon factors such as level of activity. As the heart normally pumps all of the blood received from the veins without permitting blood to dam in the venous system, cardiac output remains reasonably constant over a wide range of arterial pressure.

Cardiac Shunt

Definition

Direct connection between the two sides of the heart: In a left-right shunt the blood goes from the left side of the heart directly to the right side without passing through the body. In the more common right-left shunt, blood goes from right (the venous system) to left (arterial system) without passing through the lungs. The most common right to left shunt is a patent foramen ovale (PFO); a small residual connection between the right and left atria of the heart (uniformly present during fetal development).

►Ischemic Stroke
►Stroke

Cardioembolic/Cardiac Embolism

Definition

Sudden blocking of an artery by a clot or foreign material (embolus), which traveled through the blood stream and originated in the heart.

►Ischemic Stroke
►Stroke

Cardiovascular Mechanics

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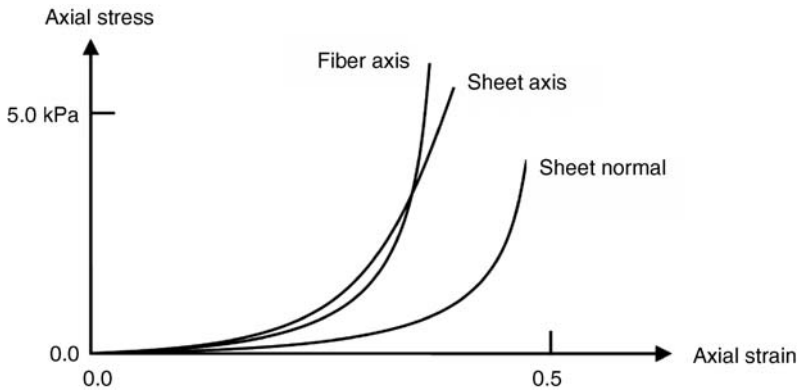
Definition

►Cardiovascular mechanics deals with soft tissue mechanics, blood flow mechanics and the coupling between these two.

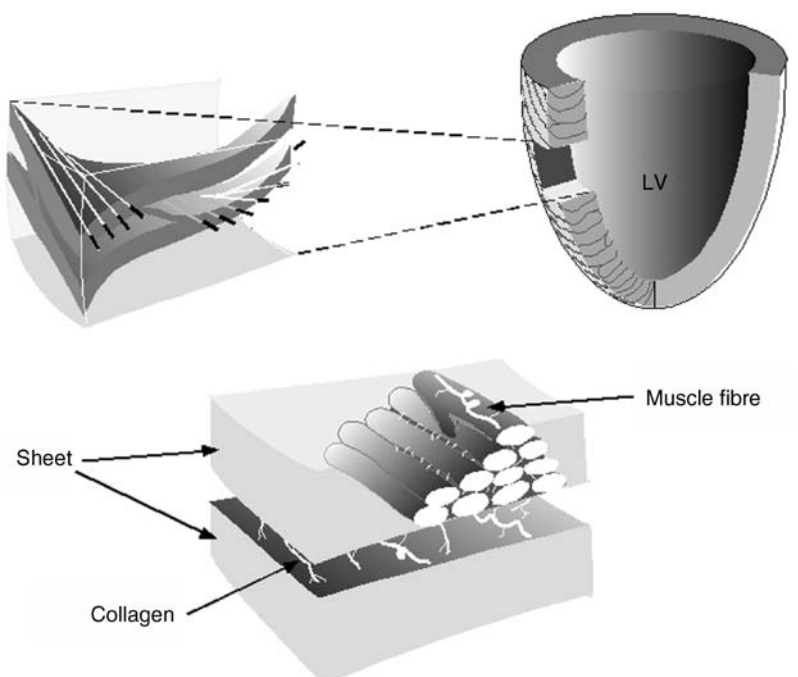
Description of the Theory

The equations governing the mechanics of both solid and fluid components are derived from the physical principles of conservation of mass and conservation of both linear and angular momentum. These equations are formulated in terms of stress tensors and either strain tensors for solid mechanics or strain-rate tensors for fluid mechanics. For the solid soft tissue component the displacements and strains are large (unlike those occurring in bone and in fact most engineering materials) and therefore the theoretical framework requires the use of large deformation elasticity theory. The relationship between stress and strain (or strain rate) is determined by the material properties of the tissue and has the following characteristics:

1. ►Stress-strain relations are highly nonlinear and typically exhibit "strain hardening" or stiffening with increased strain. This is illustrated in Fig. 1 where components of axial stress are plotted against the corresponding axial strain in experiments on a small block of myocardial tissue [1]. As the strain increases the material becomes stiffer (the slope of the stress-strain curve increases).
2. Materials are highly anisotropic, meaning that the stress-strain relationship is quite different in three orthogonal material directions [2]. This is a consequence of the material growing to support the



Cardiovascular Mechanics. Figure 1 Components of axial stress plotted against the corresponding components of axial strain for myocardial tissue [3]. The different curves correspond to the different orientations of the axial test with respect to tissue structure (see Fig. 2 and discussion below). The curve labeled "*fiber axis"* shows the change in axial stress when the tissue is stretched along the muscle fiber direction. The curve labeled "*sheet axis"* is the corresponding stress-strain relationship when the tissue is stretched in a direction orthogonal to the fibers in the plane of the sheets (see below). The curve labeled "*sheet norma"* is the stress-strain relation for stretch in a direction normal to the sheets. The fact that these curves are different for the different material directions indicates that the material is anisotropic. The J-shaped non-linear shape of these curves is a reflection of the "►strain-hardening" nature of soft tissues.



Cardiovascular Mechanics. Figure 2 Schematic illustration showing (*top*) the variation in muscle fiber direction across the wall in a segment removed from the left ventricle, and (*bottom*) the branching laminar structure of myocardium in which the sheets are composed of myocytes bound in layers 3–4 cells thick by endomysial collagen and surrounded by perimysial collagen, which also links to the adjacent sheet. This "fibrous-sheet" architecture allows for shearing to occur between the layers and aids the process of wall thickening at end-systole [4].

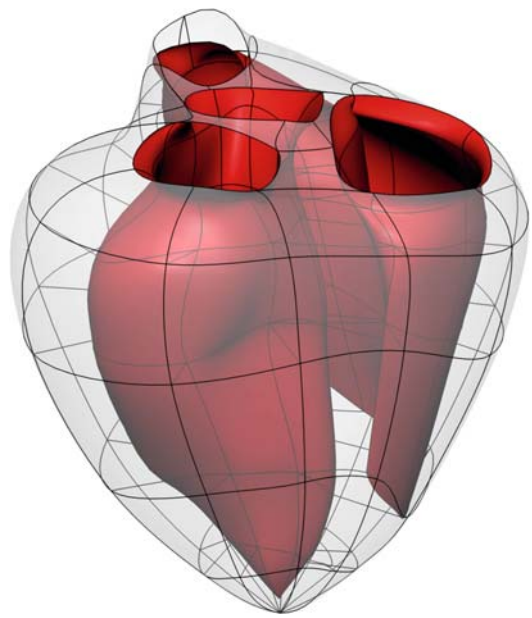
loads it is subjected to. For example, the axial stress in an artery wall, associated with tethering forces that hold the artery in position, is quite different from the circumferential stress required to support the blood pressure. The ►anisotropy of cardiac tissue can be seen in Fig. 1 where the stress-strain relations are significantly different in the three orthogonal tissue material directions [3]. The anisotropy of myocardial tissue derives from the underlying fibrous sheet structure, as illustrated in Fig. 2. Myocytes (the contractile cells in the heart) are oriented in a "fiber" direction, shown by the straight lines at the top left of Fig. 2. These cells are bound into sheets of tissue that are three to four cells thick (see lower part of Fig. 2). The sheets can shear relative to one another fairly easily (lowest curve in Fig. 1) – i.e. a given ►shear strain in this orientation produces a lower stress than a shear strain in the plane of the sheets [2].

3. The tissue properties are inhomogeneous (i.e. vary spatially), reflecting the different functional requirements of different regions. For example, the arterial walls contain three layers: (i) the innermost "intima" that contains a monolayer of endothelial cells on a basement membrane and regulates transport between the tissue and blood, (ii) the thick "media," containing smooth muscle for active contraction and bundles of collagen and elastin, which give wall the ability to store elastic energy as the wall is distended at high blood pressure and then to return this energy as the blood pressure drops, in order to maintain flow and (iii) the outer "adventia" which contains collagen, nerves and the small blood vessels that supply nutrients to the arterial wall. Similarly, the fibrous sheet structure of myocardial tissue shows ►inhomogeneity both in the orientation of the material axes across the wall of the heart (see Fig. 2 top left) and in the density of the collagen surrounding the sheets.

Both soft tissues and blood are usually considered to be incompressible (a consequence of the high water content) and for most soft tissues viscous behavior plays a small but important damping role. For the muscular components of the cardiovascular system (e.g. heart muscle and arterial smooth muscle) the mechanical function is also greatly influenced by the myofilament-generated forces that produce active muscle contraction.

Computational analysis of large deformation soft tissue mechanics is usually performed with finite element techniques, which divide the material into small coupled blocks or "elements" (see Fig. 3) and then apply integral stress balance equations to these elements. Continuous fields representing the geometric and material properties of the tissue are defined via nodal parameters, which are defined on the element boundaries and shared between adjacent elements in order to ensure continuity of the fields both within and across the elements. The equations governing blood flow are usually solved with finite element techniques, finite volume techniques or finite difference techniques. In this last case a Taylor series approximation of the governing Navier-Stokes partial differential equations produces a system of discrete equations for computation. Computational analysis of coupled solid-fluid structures is difficult and usually requires the two sets of equations to be solved simultaneously to achieve a converged solution.

A finite element mesh for the ventricular ►myocardium is shown in Fig. 3. This mesh, based on tricubic-Hermite elements is used for solving the large deformation equations of nonlinear elasticity theory. In this example the governing equations (representing conservation of mass and momentum) can be solved subject to ventricular pressure boundary conditions acting directly on the inside walls of the heart, but if these wall mechanics equations are coupled to equations governing fluid flow in the



Cardiovascular Mechanics. Figure 3 A finite element mesh used for solving the large deformation mechanics of the left and right ventricles. The surfaces shaded *red* are the internal surfaces – endocardium – surrounding the left and right ventricles, and the outer translucent surface is the epicardium. The holes at the top are the orifices regulated by the four cardiac valves – the mitral and tricuspid valves link to the left and right atria respectively and the aortic and pulmonary valves link the ventricles to the aorta and pulmonary artery, respectively.

ventricles, the boundary conditions become flow or pressure conditions specified at the flow inlets and outlets.

In some applications the finite element mesh used for solving ventricular mechanics is also used for solving reaction diffusion equations governing the spread of electrical activation through the myocardium. The equations of cardiac cell electrophysiology are based on models of the ionic currents that underlie the cardiac action potential. The cellular models can also be extended to include other aspects of cellular function, such as metabolism, pH control, signal transduction and gene regulation [7].

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Cardiovascular Reflexes

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Synonyms

Somato-cardiovascular reflexes; Viscero-cardiovascular reflexes

Definition

Cardiovascular Reflexes

The cardiovascular reflexes are those reflexes which impact cardiovascular structures (and so, functions) either through direct innervation or secondarily, for example by influencing the release of substances such as ADH.

Characteristics

There is, of course, a wealth of reflexes contributing to cardiovascular function, and a number of these reflexes are dealt with specifically in separate essays or as glossary entries in this text. The large number and the intricacy of some cardiovascular reflexes make this area of physiology challenging to understand. Sometimes this apparent complexity is augmented by the natural human tendency of students and researchers to focus so much on the fine details of specific reflex mechanisms that we fail to "see the forest for the trees." In this essay, we wish to particularly consider the principles revealed by those cardiovascular reflexes which manifest their effects via autonomic efferent neurons. We shall begin by looking at representative reflexes which are dependent upon afferent input from the cardiovascular system itself, and then expand our perspective to consider the influence of input from other organ systems.

The baroreceptor reflex, described in detail by Professor Dampney (►Baroreceptor reflex), is a well-studied reflex which demonstrates a number of important principles governing cardiovascular reflexes [1]. This reflex occurs in response to the stimulation of various subtypes of receptors located in a number of different locations in the cardiovascular system (most notably, the carotid sinus). Hence, there is a degree of *redundancy* which tends to dampen the effects of dysfunction in any one component of the afferent arm of the reflex. The reflex is *adaptive* in that it functions to maintain a fairly constant flow of blood to the brain despite alterations in blood pressure. In regard to *adaptivity*, this reflex also probably functions to optimize the efficiency of gas exchange in the lungs by increasing perfusion during inhalation. The reflex is highly *sensitive*, responding to very small changes in central blood pressure. However, it is also *adaptable* in that it permits blood pressure and ►heart rate to increase in tandem during physical exertion (►Autonomic function and exercise). The baroreceptor reflex also demonstrates another principle of autonomically-mediated cardiovascular reflexes: *reciprocal modulation* of sympathetic and parasympathetic tone. In fact, it may demonstrate this principle too well, for as we shall see, and notwithstanding popular perception, *co-activation* of sympathetic and parasympathetic output may be as common a strategy, or even a more common strategy [2].

Other cardiovascular reflexes initiated by input from within the cardiovascular system include the Bainbridge reflex, in which acute volume loading of the atria leads to sympathetically-mediated ►tachycardia, and the ►Bezold-Jarisch reflex in which excitation of ventricular receptors, especially left ventricular vagal afferents, leads to vagally-mediated ►bradycardia and vasodilation. The Bainbridge reflex may provide a mechanism of *adaptation* to increased blood volume, and is accompanied by hypothalamically-mediated strategies to reduce blood volume. The Bainbridge reflex also provides a degree of *redundancy* to the baroreceptor reflex by facilitating tachycardia during

inspiration. The Bezold-Jarisch reflex, which may contribute to dysrhythmia following, for example, ischemic damage to the ventricles, may also have an *adaptive* role in dampening the sympathetic response to orthostatic hypotension.

In addition to contributions by mechanoreceptors within the heart and great vessels, chemoreceptors in the central nervous system and in blood vessels provide important information on blood gases and pH leading to reflex modulation of circulatory function (and, of course, respiratory function as well).

Non-cardiovascular ►visceral afferents, such as those in the respiratory and digestive systems, also have the capability of influencing cardiovascular function. The integration of afferent input from different visceral organs occurs most notably in the nucleus of the solitary tract (NTS) [3]. Hence, stimuli signaling metabolic demand in particular viscera will result in reflex alterations in sympathetic outflow to the corresponding vascular beds in order to facilitate appropriate perfusion. Conversely, noxious stimulation of afferents within the airways of the respiratory system often results in bradycardia and systemic (as well as pulmonary) hypertension – a reflex which, in conjunction with changes in ventilatory behavior, likely inhibits the uptake of noxious chemicals into the blood stream.

Bradycardia with hypertension suggests *co-activation* of sympathetic and parasympathetic efferents, a pattern characteristic of the trigeminocardiac reflexes [2]. These are a family of cardiovascular reflexes involving afferent stimulation within the distribution of the trigeminal nerve, and the most familiar example is the so-called "diving reflex." This phenomenon, triggered by immersion of the face in cold water (or even cold air blowing on the face), manifests as apnea, bradycardia and hypertension – a highly *adaptive* strategy when submerged! Interestingly, the oculo-cardiac reflex, initiated by stimulation within the distribution of the ophthalmic branch of the trigeminal nerve, is characterized by hypotension – a response which is more common when confronted with noxious visceral stimulation, particularly deep pain.

Cardiovascular reflex responses to noxious stimulation, especially noxious somatic stimulation, have been well-characterized [4] and are discussed elsewhere in this text by Dr. Uchida (►Somato-autonomic reflex). Normally, noxious stimulation of somatic tissues leads to tachycardia and systemic hypertension – the "fight or flight response" – leading to increased ►cardiac output with obvious *adaptive* significance. In detail, however, the responses of different vascular beds are specific rather than stereotypical, and may be influenced by coincident innocuous stimulation. In simpler terms, pain does not necessarily lead to wholesale sympathetic activation, but rather a tailored response. Innocuous somatic stimulation, conversely, is often, but not invariably, associated with reduction in heart rate and blood pressure attributed to increased vagal tone (►Vagus nerve) and decreased sympathetic tone. However, the precise response is *adaptable* and will be influenced, for example, by the site, modality and psychosocial context of the stimulation.

Cardiovascular reflexes may also be initiated or modulated by information concerning body position and movement, especially information from the vestibular system [5]. A role has also been postulated for postural information from paraspinal muscles, and in humans, this would particularly include the muscles of the neck [6].

Higher Level Structures

In humans, reflex sympathetic output to the cardiovascular system originates most immediately in the rostral ventrolateral medulla (VLM), and incorporates input from the hypothalamus and brain stem nuclei [1,3] (►Central regulation of autonomic function). Specifically, parvocellular neurons of the paraventricular nucleus of the hypothalamus project both to the rostroventrolateral medulla and directly to spinal sympathetic preganglionic neurons (SPNs). Neurons of the rostral ventrolateral medulla are arranged in clusters which project in a topographic, and therefore viscerotropic, fashion to sympathetic preganglionic neurons. Hence, stimulation of more cephalad cell clusters may result in constriction of the renal vascular bed, whereas stimulation of more caudal cells results in constriction of mesenteric and hind limb muscle vascular beds. The VLM neurons project primarily to the intermediolateral cells columns of the thoracic cord, and release catecholamines and L-glutamate to excite spinal SPNs [7]. Within the spinal cord, the activity of some SPNs is inhibited by nitric oxide and glycine, although the effects of nitric oxide are complex and involve multiple pathways in the spinal cord.

Parasympathetic innervation to the heart originates in the dorsal vagal motor nucleus and the nucleus ambiguus. Neurons in the dorsal vagal motor nucleus, stimulated directly by the nucleus of the solitary tract (NTS), are probably of less importance to cardiac function than neurons of the nucleus ambiguus, which are indirectly stimulated by the NTS via the caudal VLM. Increased input to the NTS from baroreceptors brings about reflex attenuation of heart rate via vagal stimulation. The dorsal vagal motor nucleus and nucleus ambiguus are also the source of relatively sparse parasympathetic innervation to vascular beds in a variety of organs.

Lower Level Components

As somatic and visceral afferents are dealt with in depth elsewhere in this text, below we will particularly consider

the lower level efferent components of cardiovascular reflexes, dealing first with sympathetic motor neurons and then parasympathetic motor neurons.

Spinal sympathetic preganglionic neurons are located principally within the intermediolateral and, to a lesser extent, intermediomedial columns of the thoracic and upper lumbar spinal cord [7]. In humans, some SPNs are also located within the central autonomic nuclei and the lateral funiculus. The cells of the spinal sympathetic nuclei are not uniformly distributed, but rather are arranged in nests along the length of the thoracic and upper lumbar cord. Axons from each cluster of SPNs exit the spinal cord mainly through the immediately adjacent nerve roots and so project to particular peripheral targets. Upper thoracic SPNs, the overwhelming majority arising from the first to fifth thoracic levels, project to the heart, particularly the ventricles, via the cervical sympathetic ganglia (►Autonomic ganglion). Additionally, SPNs along the length of the thoracolumbar spinal cord also project in a segmentally-organized fashion to adjacent vascular beds.

The cell bodies of postganglionic neurons within the cervical sympathetic ganglion are arranged in a topographical fashion and form morphologically distinct clusters [7]. Hence, by way of example, stellate ganglion cells projecting to the heart may be distinguished from SPNs to, for example, the vascular bed of the sternocleidomastoid muscle.

Cardiac sympathetic nerves arising from the left and right cervical sympathetic chains and ganglia cross (and sometimes cross back again) from left to right on their journey to the heart [8]. Furthermore, it is apparent, and consistent with their anatomical targets, that left and right autonomic nerves serving the heart are functionally distinct. In particular, sympathetic fibers arising from the left stellate ganglion appear to have a greater influence on heart rate and heart rate variability, such that excessive activity of fibers from the left stellate ganglion or loss of modulating influences from the right stellate ganglion favor arrhythmogenesis.

The cardiac vagus nerve consists of parasympathetic preganglionic fibers which project through mixed sympathetic and parasympathetic plexi to parasympathetic ganglia close to or in contact with the heart. From these ganglia, postganglionic fibers course to the electrical conduction system of the heart and, to a lesser extent, to the myocardium [9]. In histological sections of human heart, the greatest concentration of acetylcholinesterase-positive cells is seen in the region of the sinoatrial node, with concentrations diminishing through the atrioventricular node, the atrioventricular bundle and into the bundle branches. In general, parasympathetic innervation of the sinoatrial node is predominantly from the right vagus nerve, while innervation of the atrioventricular node is predominantly from the left vagus nerve.

Higher Level Processes

Autonomic output to the cardiovascular system originates from the interaction of a number of components of the central nervous system (►Central regulation of autonomic function). In particular, the nucleus tractus solitarius (NTS) integrates sensory input from the viscera with information from higher brain centers in order to synthesize output to other brainstem and spinal reflex centers [1]. A portion of visceral afferent input to the NTS projects in a viscerotropic fashion such that information from particular organs projects to specific nuclei within the NTS. The anatomical basis therefore exists for reflex responses which are influenced by the current afferent input from particular visceral organs.

Baroreceptor afferents (►Baroreceptor reflex), which provide beat to beat information on cardiovascular function, project particularly to the intermediate (general visceral) region of the NTS. From the NTS afferent information of different types is relayed to various centers including the insular cortex (the primary viscerosensory cortex), the periaqueductal gray (PAG) of the midbrain, the parabrachial region of the pons, and the ventrolateral medulla. Baroreceptor information is especially relayed to the caudal then rostral ventrolateral medulla and cardiovagal neurons. Receptors similar to those of the carotid sinus, but perhaps less studied, have also been identified in the aortic arch and the myocardium, and pulmonary and thoracic stretch receptors also have a small role in modulating the rhythmicity of central autonomic neurons. There may also be a very short feedback loop by which intrinsic cardiac neurons increase their activity in response to local mechanical stimulation. Some vascular and pulmonary baroreceptors convey afferent information via the vagus nerve giving this nerve an afferent and efferent role in the reflex regulation of the cardiac cycle. Visceral pain and perhaps some baroreceptor information may also ascend via the spinothalamic, spinoreticular and spinomesencephalic pathways to influence baroreceptor reflex behavior. Noxious input, and so activation of the PAG, tends to dampen baroreflexes by augmenting the activity of cardiac sympathetic efferents. Conversely, baroreceptor excitation also depresses somato-cardiac sympathetic reflex responses to A- and C-fiber excitation [4].

Sensory input from the viscera may also be influenced at the level of the primary afferent by convergence with information from somatic tissues, including convergence of thoracic somatic and cardiac afferents onto single spinal neurons. Histological and physiological data also indicate projections of somatic afferents to visceromotor centers. The implied interaction is self-evident in, for example, cardiovascular responses to pain, and involves, at least in part, projections via the periaqueductal gray to the rostral ventrolateral medulla.

In preparation for increased demand on the cardiovascular system, anticipatory "central command" may increase heart rate and blood pressure prior to signaling of work from receptors within the muscle (►Autonomic function and exercise). Additionally, chemoreceptors and mechanoreceptors within muscle signal ongoing exercise. However, input from large diameter group 1a and 1b afferents generally has little influence on cardiovascular function. Central projections and effects of afferent input from neck muscles may represent a special case. Some low-threshold somatic afferents from the neck region project directly to the vestibular nuclei and thereby modulate vestibular influences on cardiovascular function. There is also physiological evidence of more direct connections between cervical muscle afferents and autonomic motor neurons; specifically, projection of muscle afferents directly to spinal sympathetic preganglionic neurons. These results suggest a special role for afferent input from axial muscles, especially those of the neck [6]. The adaptive rationale for these interconnections would include maintenance of appropriate blood pressure and blood volume distribution during postural changes.

Lower Level Processes

Within the heart, the sympathetic efferents innervate many targets. Human heart contains subtypes of α_1, α_2, β_1 and β_2-adrenergic receptors. β-adrenergic receptor subtypes are the more abundant and their stimulation generally results in increased heart rate and increased force of contraction. Although these receptors are fairly evenly distributed throughout the atria and ventricles, the sinoatrial node is especially richly invested [10]. Both of α and β-adrenergic receptors are also found on vascular smooth muscle. Stimulation of α-adrenergic receptors leads to vasoconstriction, whereas the stimulation of β-adrenergic receptors on skeletal muscle and liver vasculature leads to vasodilation.

The effects of vagal stimulation on the heart have been attributed primarily to the release of acetylcholine and somatostatin. A number of subtypes of muscarinic acetylcholine receptors are found in the mammalian heart. The M2 subtype is the most abundant muscarinic receptor in human myocardium, and is more abundant in atrial than ventricular tissue.

While parasympathetic innervation of blood vessels is sparse when compared with sympathetic innervation, M3 muscarinic receptors are found in vascular endothelium. Activation of endothelial muscarinic receptors leads to the production of NO which diffuses into adjacent smooth cells initiating vasodilation.

Process Regulation

It has been argued that as a result of integration of information from diverse receptors, cardiovascular reflexes are fundamentally adaptive and adaptable to the unique circumstances in which they arise in each individual. Interestingly, however, at the level of the spinal nuclei, virtually all stimuli result in what could be regarded as excitatory reflexes. Hence, both noxious and innocuous stimulation at any given site will initiate responses characteristic of "fight or flight." It is the influence of descending excitatory and inhibitory pathways which then modulates (facilitates or depresses) the spinal reflexes in order to produce the final response most appropriate to the subject's current circumstances [4]. The coordinated regulation of cardiovascular reflexes is most easily appreciated when the harmonious interaction of supraspinal and spinal components is disrupted by spinal injury, as described briefly below.

Function

Collectively, the cardiovascular reflexes are designed to partition a limited blood supply among tissues with changing and often competing demands. Furthermore, this task must be accomplished in a dynamic creature whose movements may impose sudden gravitational challenges on the partitioning of the blood (not to mention other fluids and tissues of the body). The remarkable success of reflex regulation of cardiovascular function owes much to the effectiveness of the central nervous system in integrating afferent input from many sources: the cardiovascular system itself, other viscera, the somatic tissues of the musculoskeletal system and skin, and of course input from higher centers of the nervous system itself (►Homeostasis).

Pathology

Cardiovascular reflexes come to clinical attention most often when pathology prevents their appropriate expression, for example when autonomic failure leads to phenomena such as orthostatic hypotension. However, the reflexes may themselves become pathological when dysfunction occurs in the afferent or efferent arms of the reflex pathway, or when there is an error in central processing. This occurs most dramatically in autonomic dysreflexia (►Autonomic/enteric dysreflexia) following high spinal cord injury. Often following high spinal cord injury, more caudal spinal autonomic reflex centers are liberated from descending inhibition. Additionally, new and inappropriate synapses may form following injury and this may facilitate overexuberant cardiovascular responses to somatic or visceral stimulation. Clinically, this may manifest as paroxysmal hypertension, which is an important source of morbidity and mortality in spinal patients.

Therapy

Cardiovascular reflexes see little application in conventional western medicine. Clinicians, and patients themselves, may occasionally take advantage of the

oculo-cardiac reflex or the baroreceptor reflex (by applying pressure to the eyes or the carotid bifurcation) to transiently attenuate hypertension or palpitations. In various forms of traditional medicine, however, innocuous or noxious stimulation may be applied to the skin (for example, via acupuncture) or muscles (for example, via mobilization or manipulation) with the intent of effecting long-term changes in cardiac function, systemic blood pressure or perfusion of particular vascular beds. The clinical effectiveness of these approaches is largely untested.

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Carotid Angioplasty and Stenting

Definition

This is a possibile alternative to carotid endarterectomy to treat narrowing in the carotid artery: A carotid stent is a small metal mesh tube that is inserted into the carotid artery via a catheter inserted through the femoral artery.

The stent is advanced up to the carotid artery and expanded, thus the narrowed carotid artery is widened (sometimes with the assist of a small ballon inflation, i.e., angioplasty).

►Ischemic Stroke
►Stroke

C

Carotid Body Chemoreceptors and Respiratory Drive

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Synonyms

Peripheral chemoreceptors; Respiratory rhythmogenesis

Definition

The carotid bodies (CBs) are peripheral chemoreceptors that detect changes in arterial blood O_2, CO_2, pH, glucose and temperature and provide a key source of stimulation to brainstem respiratory centers.

Characteristics

Introduction

Carotid bodies (CBs) are peripheral arterial ►chemoreceptors located in the neck that detect changes in PO_2, PCO_2, pH, temperature and glucose in arterial blood. The importance of the CB to the control of breathing was first revealed by the Belgium physiologist, Corneille Jean Francois Heymans. Heymans discovered that cutting the neuronal connections between the carotid body and brainstem caused breathing to slow (hypoventilation) in the resting state and eliminated fast breathing (hyperventilation) caused by creating a local hypoxia-like situation by injecting cyanide into the CB circulation. These experiments demonstrated an essential role for the CBs in maintaining normal arterial carbon dioxide levels and initiating the primary respiratory and cardiovascular physiological responses to hypoxia. In 1938, Heymans was awarded the Nobel Prize for his discovery, arguably one of the most significant in respiratory research to date.

Overview of the Carotid Body

Anatomy, Morphology, Innervations and Blood Supply

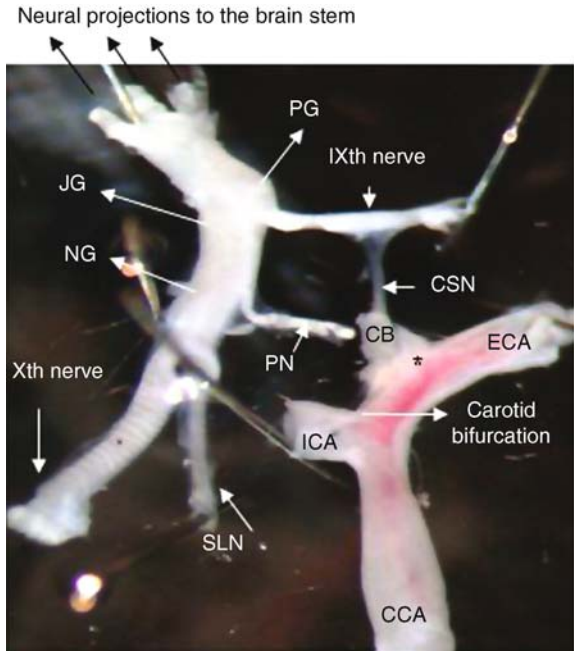
Oxygen is sensed by almost all mammalian cells (excitable and non-excitable), but the principle sensors, those with the greatest sensitivity and capability of initiating systemic responses, are the carotid bodies (CBs). While the CBs are the principle oxygen sensors, they also participate in the regulation of carbon dioxide, pH, temperature and glucose. The CBs are paired organs located bilaterally at each of the common carotid bifurcations in the neck (see Fig 1). This is a strategic location, between the heart and brain, two of the most oxygen-dependent organs.

The CBs vary in size and weight depending upon species. In humans, a normal CB measures 3–5 mm in diameter but the CBs are often larger in people living at higher altitudes. The histological appearance of the CB includes two types of cells: glomus cells (also known as type I cells) and sustentacular cells (also called type II). Glomus cells are the primary oxygen sensors. There are ~9,000 and ~60,000 glomus cells in the rat and cat, respectively. Glomus cells are embryologically derived from the ►neural crest, are electrically excitable and have globular cell bodies usually 8–15 μm in diameter. Ultrastructural studies have shown that the glomus cell cytoplasm contains dense as well as clear cored vesicles that actively synthesize and package neurotransmitters, e.g., catecholamine, acetylcholine. They also have an abundance of mitochondria which explains the comparatively high oxygen consumption measured for CB tissue. Groups of 5–10 glomus cells are typically arranged into clusters surrounded by 2–3 sustentacular cells and separated from other clusters by blood vessels. Recent evidence suggest that glomus cells are electrically coupled, and that coupling is modulated by hypoxia.

The principal sensory innervation of glomus cells is via the carotid sinus nerve (CSN), a branch from the glossopharyngeal nerve (GPN; IXth ►cranial nerve) which carries ►afferent signals to the brainstem respiratory center. The afferent nerve endings on glomus cells are part of neurons whose cell bodies are located in the petrosal ganglion (Fig. 1).

Such nerve endings comprise more than 95% of the nerve endings on glomus cells. The CB also receives sensory innervation from the jugular and nodose ganglia. Recent investigations have shown that CBs receive efferent innervation from nNOS (neuronal nitric oxide synthase)-containing neurons located in the GPN and CSN. In addition, carotid afferent neural discharge is also regulated by ►efferent fibers from the ►sympathetic supply of the superior cervical ganglion (SCG), through the ganglioglomerular nerve. These efferent pathways are generally considered to be inhibitory to the CB.

Blood vessels comprise nearly 20% of the total volume of the CB, consistent with the organ's enormous blood flow (about 40 μl/min per cat CB or more than 2 l/min/100g). In most species the CB's blood flow comes from the external artery or its branches. In the rat a single CB artery usually arises directly from the external carotid artery near the bifurcation of the common carotid artery or from the occipital artery, but in the cat the source of the vessel is quite variable. Arterio-venous (A-V) ►anastomoses play an important role in regulating blood flow within the CB during hypoxia. A rise in sympathetic nerve activity during hypoxia causes a redistribution of blood flow in the CB, with a-v anastomoses diverting arterial blood from regions of glomus cells with a high metabolic rate to regions of low metabolism.



Carotid Body Chemoreceptors and Respiratory Drive. Figure 1 Photograph of an *in vitro* CB with other surrounding structures from a neonatal rat. *PG*, petrosal ganglion; *NG*, nodose ganglion; JG, jugular ganglion, *CB*, carotid body; *ECA*, external carotid artery; *ICA*, internal carotid artery; *CCA*, common carotid artery; *PN*, pharyngeal nerve; *SLN*, superior laryngeal nerve; *CSN*, carotid sinus nerve. IXth nerve, grossopharyngeal; Xth nerve, vagus. *The occipital artery was severed to make the CB visible.

Carotid Body Responses to Hypoxia

Acute Versus Chronic. Mechanisms of Oxygen Sensing in the CB. Integration of the Hypoxia Signaling Pathway Within the CB from Sensors to Couplers (Signaling Molecules) to Effectors

Oxygen deprivation/low ►partial pressure of oxygen, or ►hypoxia, can arise from many physiological as well as pathological situations. It is widely accepted that

glomus cells of the CB are the primary site for oxygen sensing and that hypoxia causes their depolarization, triggering neurotransmitter release. However, the precise details need to be worked out. As reviewed in the following sections, CB responses to hypoxia can be acute (time scale of seconds to minutes) or chronic (time scale of hours to days). Further, there are various proposed mechanisms for oxygen sensing and multiple signaling pathways that may be involved in mediating the CB responses to hypoxia.

Acute Responses

During normoxia (100 Torr PO_2) CSN shows mild levels of activity. Activity is almost abolished at higher levels of PO_2 (>200 Torr) but increases exponentially as the level of PO_2 is decreased. Studies using isolated CB preparations suggest that the response to a bout of hypoxia can be multiphasic. Accordingly, activity reaching a maximum within the first few minutes of hypoxia, and then declines slightly but remains elevated for the remainder of the bout (*sensory hypoxic decline*). Following termination of the bout, CSN activity falls below that preceding the bout (*sensory post-hypoxic decline*). Augmentation occurs when multiple bouts occur in succession (sensory augmentation) and under some stimulus paradigms it's possible to induce long lasting increases in baseline activity (*sensory long term facilitation*). Whether these responses contribute to similar time-dependent ventilatory responses remains to be determined.

The richness of the acute response of the carotid body to hypoxia, may reflect the complexity of the organ which is endowed with a plethora of neurotransmitter and neuromodulator systems and involves the possible interaction of multiple oxygen sensing mechanisms, as summarized below:

Metabolic or Mitochondrial Pathway

The metabolic hypothesis was originally proposed by [1] and eventually developed by [2] The hypothesis states that due to less oxygen (during hypoxia) electron transport from the substrate to oxygen through the ►mitochondrial respiratory chain is retarded, as a result the electron carriers (i.e., different complexes) operate in more reduced states. This inhibits ►oxidative phosphorylation, increases ►NADH concentration and decreases ►ATP production leading to an increase in mitochondrial matrix H^+ concentration. Eventually, the mitochondria depolarize, triggering calcium release from the endoplasmic reticulum-mitochondrial stores that eventually results in plasma membrane depolarization and neurotransmitter release. In support of the mitochondrial hypothesis, high concentrations of carbon monoxide [CO; a complex IV inhibitor; partial pressure of CO (Pco) > 300 Torr] during normoxia augment CB sensory discharge in the dark and mimic hypoxia. Consistent with the hypothesis, the CO-induced increase is reversible by white light, with the photochemical action spectrum of the light effect on sensory activity matching the absorbance spectrum of the ►cytochrome aa_3 – CO complex. Further, mitochondrial inhibitors, like rotenone (complex I inhibitor), antimycin (complex III inhibitor), cyanide (complex IV inhibitor), and oligomycin (ATP - synthase inhibitor) transiently increase CB chemosensory activity and abolish the hypoxic response. According to this hypothesis, the terminal oxidase of the mitochondrial respiratory chain within glomus cells, cytochrome aa_3 (a heme protein), is different from that in other tissues, having an unusually low affinity for oxygen. This low affinity makes the CB cytochrome aa_3 more sensitive to slight falls in oxygen, and hence a likely candidate for an oxygen sensor.

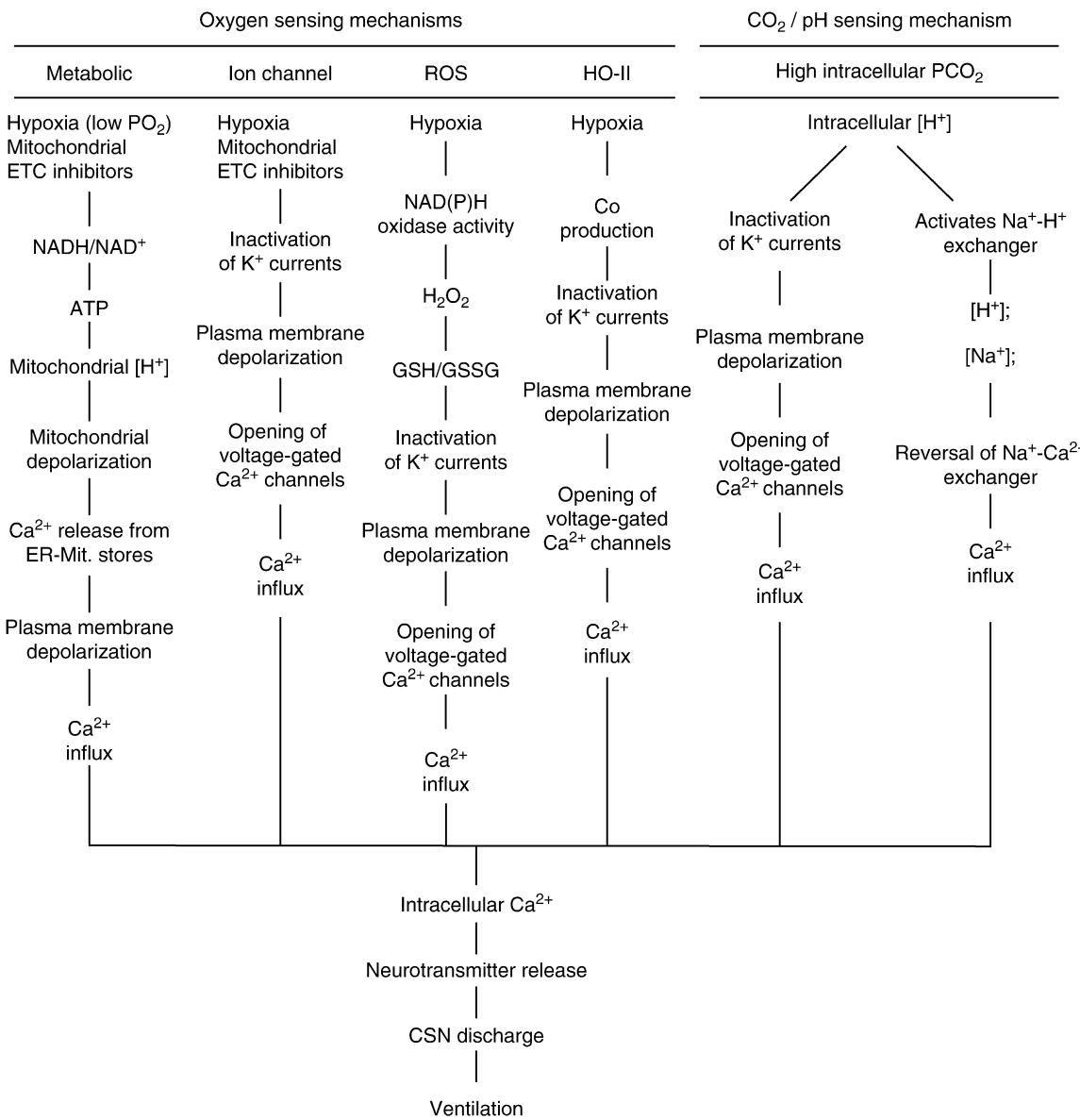
Membrane or Ion Channel Pathway

[3] from Spain were the first to enunciate this hypothesis. According to this hypothesis, the immediate O_2 sensor is coupled directly to K^+ channels situated within the plasma membrane of glomus cells, the seminal biophysical change during hypoxia being a reduction in the conductance of these channels, leading to cell depolarization. Various types of K^+ channels have been identified in CB glomus cells that demonstrate a reduction in conductance in the presence of hypoxia, but their relative importance in oxygen sensing is likely to be species dependent. These include: (i) ►Ca^{2+} insensitive, voltage-dependent transient K^+ channels (IK_V); (ii) ►Ca^{2+} sensitive, voltage-dependent K^+ channels (IK_{Ca}) - similar to large conductance BK-type channels; (iii) Voltage insensitive TASK-like ►leak K^+ channels - active around the resting membrane potential of glomus cells; and (iv) ►HERG-like K^+ channels.

It is worth mentioning that the mitochondrial and ion channel hypotheses are not mutually exclusive and may act synergistically to regulate CB neural discharge (see Fig. 2).

ROS Hypothesis

[4] postulated that NADPH oxidase, a heme-containing enzyme present in the CB glomus cells, produces reactive oxygen species (ROS) such as H_2O_2 during normoxia. Hypoxia reduces the activity of the enzyme, leading to a decrease in H_2O_2 production. According to the ROS hypothesis, a decrease in H_2O_2 production results in an increased ratio of reduced to oxidized glutathione (GSH/GSSG), which in turn reduces the opening probability of the K^+ channels in the plasma membrane, leading to depolarization of the glomus cells. In support of this hypothesis, diphenyliodinium (DPI), an inhibitor of NADPH oxidase, augments CB basal activity and blocks further augmentation by



Carotid Body Chemoreceptors and Respiratory Drive. Figure 2 Proposed models of O_2 and CO_2/pH sensing in the CB. Arrows upward and downward indicate increase and decrease respectively. *ROS*, reactive oxygen species; *HO*-II, heme oxygenase–II; *ETC*, electron transport chain.

hypoxia. Thus, NAD(P)H oxidase may serve as an oxygen sensor.

Heme Oxygenase-2

Membrane bound heme oxygenase –II (HO-II) immunoreactivity has been reported in glomus cells. In normoxia, HO-II likely breaks down heme oxidatively to iron, biliverdin and CO. This endogenous CO has the capability of exerting an excitatory influence on large conductance K^+ channels (BK channels) reducing the excitability of the glomus cell. Thus, according to the hypothesis, oxygen becomes rate limiting for the HO-II during hypoxia and CO production is reduced which, inturn, reduces the conductance of the BK channels leading to depolarization of glomus cells. In support of this hypothesis, HO-II inhibition by Zn-protoporphyrin–IX blocks endogenous CO and augmented the CB chemosensory activity [5]. This is consistent with the inhibition of chemosensory activity during hypoxia in the presence of low levels of CO. Hence, HO-II has now been claimed as an oxygen sensor.

The final consequence of hypoxic-modulation of the glomus cell function is neurotransmitter release.

The conventional neurotransmitters involved include catecholamines, ATP and acetylcholine.

ATP

Increasing evidence suggests that the purines, ATP and adenosine, make key contributions in CB hypoxic signaling. Glomus cells release ATP in response to hypoxia which can stimulate P2X receptors on afferent terminals, elevating intracellular Ca^{2+} and producing excitatory responses. The ATP released from the glomus cells can also be dephosphorylated to adenosine by a series of extracellular enzymes, which in turn can stimulate A_1, A_{2A} and A_{2B} adenosine receptors. When stimulated, these receptors increase ventilation rate. Prolonged hypoxic challenge can alter the expression of purinergic receptors, suggesting a role in hypoxic adaptation.

Acetylcholine (ACh)

Glomus cells express the enzymes necessary for the generation and inactivation of ACh. Hypoxia results in release of ACh in cat CBs, however in rat and rabbit CBs hypoxia inhibits the basal release of ACh. ACh has both excitatory and inhibitory effects within the carotid body, mediated by nicotinic ands muscarinic ACh receptors, respectively. The relative abundance of the nACh and mACh in the CBs varies among species leading to different species-dependent effects of ACh on CSN discharge.

Catecholamines

Glomus cells from cat, rabbit and rat CBs express tyrosine hydroxylase (TH) and dopamine β hydroxylase, (DBH) the enzymes responsible for the synthesis of dopamine (DA) and norepinephrine (NE), respectively. Both DA and NE are released from glomus cells in response to hypoxia in a Ca^{2+} dependent manner, though DA would appear to be released preferentially. Both catecholamines are considered to be inhibitory to CB. Blockade of dopaminergic receptors for example usually potentiates the response to hypoxia.

Chronic Responses

Long lasting changes in the CB morphology and functioning are evident in chronic sustained and chronic intermittent hypoxia. One of the many physiological adaptive responses to ►chronic sustained hypoxia is ►ventilatory acclimatization to hypoxia (VAH). VAH occurs most frequently in mountaineers that ascend to high altitudes (low environmental Po_2) or in patients suffering from severe obstructive pulmonary diseases (resulting in hypoxemia). VAH is manifested as a hyperventilation over and above the acute response to the same level of hypoxia. Plasticity within the CB likely plays an important role in VAH. A number of morphological and biochemical alterations in the CB are associated with chronic hypoxic exposure including hyperplasia of the glomus cells, increased vascularization, hypertrophy of the CB and increased catecholamine levels. Recent evidences suggest that some of these effects may involve hypoxia inducible factor-1 (HIF-1) [6]. The net result is a long-lasting, but reversible increase in the CB response to hypoxia. Interestingly, individuals born and raised in hypoxic environments show blunted hypoxic ventilatory responses. ►Chronic intermittent hypoxia (IH) occurs during periodic breathing experienced by sojourners sleeping at high altitude and humans suffering from obstructive and central apneas. While longterm effects of intermittent hypoxia on the ventilation of animals have been well documented, only recently have the longterm effects of intermittent hypoxia on ventilation in humans been reported. While most animal data points to a direct effect of IH on structures within the brainstem, increasing evidence suggesting that IH may also causes an increase in CB sensory activity that persists in normoxia, resembling long term facilitation (LTF) of breathing [7].

CO_2/pH Sensing in the CB

As demonstrated by Heymans, the CB is also a principal pH/Pco_2 chemoreceptor involved in ventilation. They compliment additional sets of CO_2/pH-sensitive cells located in the brainstem, cerebellum and hypothalamus, known as the central respiratory chemoreceptors. However, the relative contribution of the CBs and central respiratory chemoreceptors remains hotly debated [8]. A simple view is that the CBs provide the rapid response, but the central chemoreceptors provide most of the steady-state response. However, as Heymans demonstrated, transecting the CSN leads to hypoventilation, an increase in arterial PCO_2 and a resulting respiratory acidosis. Thus, while the CB's are vital for maintaining normal PCO_2 the central chemoreceptors alone are insufficient.

There are two opposing hypothesis as to how hypercapnia (increase in partial pressure of CO_2)/fall in intracellular pH might elevate intracellular calcium and trigger CSN activity (Fig. 2): (i) Intracellular acidosis or hypercapnia inhibits membrane K^+ channels, causing cell membrane depolarization and leading to Ca^{2+} entry through voltage-gated channels. (ii) Intracellular acidosis activates the $Na^+ - H^+$ exchanger system, extruding H^+ and increasing Na^+ influx. This results in a rise in intracellular Na^+ and subsequent Ca^{2+} influx through the reversal of the Na^+–Ca^{2+} exchanger.

Importance of the CB in Health and Disease

Oxford Fan

Hypoxic blood is often accompanied by alteration of Pco_2. At the organ/cellular level, low O_2 and high CO_2 interact synergistically to stimulate glomus cells ($O_2 - CO_2$ stimulus interaction); the effects of hypoxia and hypercapnia applied simultaneously are greater

than the sum of these two stimuli when applied separately to the CB. As the Po_2 levels decline, the relationship between the sensory afferent nerve activity and Pco_2 becomes increasingly steeper, leading to enhanced ventilatory reflexes.

Living Without Carotid Body/Carotid Body Denervation

Carotid body denervation (CBD) in neonates results in significant mortality owing to hypoventilation, irregular breathing and long apneas. These effects seem to be age dependent. In adults, loss of CBs in otherwise healthy individuals is not acutely life threatening despite the resulting hypoventilation and loss of hypoxic response. In fact in, CBD survivors there is enough redundancy and plasticity in the control of breathing to eventually compensate for most of the consequence of CBD. One site of plasticity is the oxygen chemoreceptors of the aortic arch which change from having a weak to significant effect on ventilation.

Chronic Mountain Sickness

Humans living at altitudes are exposed to chronic hypobaric hypoxia and some suffer from chronic mountain sickness. The morphological alterations of the carotid bodies in people living at high altitudes are well known (see Section 3, Chronic response above). These may be adaptive, increasing the responsiveness of the carotid body to sustained hypoxia and therefore incomplete CB adaptation may exacerbate the likelihood of mountain sickness.

Sleep Apnea

A substantial population of humans experience chronic intermittent hypoxia as a consequence of recurrent ►apneas during sleep. People with recurrent apneas are prone to hypertension, myocardial infarctions, metabolic syndrome and even stroke. The chemoreceptor gain of the carotid body in these patients is elevated, which may contribute to the cause of periodic breathing and the excitation of the carotid body during apnea is a primary cause of hypertension.

Acute Respiratory Distress Syndrome (ARDS) and Chronic Obstructive Pulmonary Disease (COPD)

Patients suffering from ARDS and COPD have profound morphological alterations in the carotid body. In some rare diseases, such as the ►congenital hypoventilation syndrome and the ►sudden infant death syndrome, anatomical and biochemical abnormalities of the carotid body have been shown.

Unanswered Questions and Broad Range of Research Opportunities in CB Chemoreceptor Physiology

1. Relative contribution of different O_2-sensing molecules to glomus cell excitability.
2. Understanding interaction between oxygen and carbon dioxide sensing within the CB.
3. Understanding sustentacular-glomus cell interactions.
4. Modulation of the CB function by ►efferents.
5. Characterization of the signaling pathway from CB to the brainstem respiratory controller.
6. Understanding system-level interactions between peripheral and central chemosensors.

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Carotid Chemoreflex

►Respiratory Reflexes

Carotid Endarterectomy

Definition

Is the surgical procedure whereby the carotid artery is opened and the atherosclerotic plaque inside removed.

Indicated after a stroke if the carotid artery is narrowed >70%.

►Ischemic Stroke
►Stroke

Carpal Tunnel Syndrome

Definition

Characterized by numbness and paresthesias in the palm and pain up the forearm due to nerve entrapment of the median nerve in the carpal tunnel at the wrist.

Cartesian Dualism

Definition

The view, deriving from René Descartes in the seventeenth century, that mind and body are fundamentally different sorts of things, distinct from one another and independent.

►Reductionism (Anti-Reductionism, Reductive Explanation)

Cartilage

Definition

The thin avascular tissue that lines the ends of bones in synovial joints.

►Joints

CASK

Definition

Calcium/Calmodulin-associated serine/threonine kinase. A multi-functional adaptor protein that appears to serve a scaffolding function in the synapse and to recruit/organize other signaling molecules. At the synapse, key binding partners include Mint and Velis, as well as neurexins.

►Synaptic Proteins and Regulated Exocytosis

Caspase

Definition

Caspase is an acronym that stands for cysteine-aspartate protease. Caspases are proteolytic enzymes that contain a cysteine residue in the catalytic site and cleave their substrates at a consensus motif, Asp-Glu-Val-Asp. It plays a pivotal role in apoptosis by cleaving key substrates.

Cataplexy

Definition

Sudden loss of muscular tonus**.** Occurs in narcolepsy.

►Neuroendocrinology of Eating Disorders

Catastrophic Inference

Definition

One of the problems that arise during the training process of an artificial neural network is catastrophic inference, in which a task being learned overwrites previous learning. As network weights are adjusted to improve performance on the new task, performance on a previous task that relied on the old set of weights decreases, often catastrophically. This has presented a challenge to the application of connectionist simulations as models of biological or psychological data.

►Connectionism

Catatonia

Definition

Usually defined as a subtype of schizophrenia characterized by dominance of psychomotor symptoms such as lack of movements (stupor) or speech (mutism) frequently associated with extreme anxiety. Similar symptoms can also be encountered in patients with severe depression and in patients with organic brain lesions.

►Schizophrenia

Catch-Up Saccade

Definition

A saccade elicited when smooth pursuit eye movements (SPEM) lag behind a moving target because of limitations of SPEM velocity, acceleration, or frequency response. As long as such conditions apply, catch-up saccades repeatedly eliminate the resulting lag (in the rare case of too fast SPEM, the resulting lead is reduced by back-up saccades). Their amplitude is determined by the position and velocity errors of the eye with respect to the target sampled about 120 ms prior to saccade occurrence, with the velocity-related component predicting the increase in position error by the time of saccade occurrence. SPEM is being continued during catch-up saccades and its velocity adds to theirs.

►Oculomotor Control
►Saccade, Saccadic Eye Movement
►Smooth Pursuit Eye Movements

Catecholamines

Definition

Catecholamines are dihydroxylated biologic amine compounds derived from the amino acid L-tyrosine. The most important biogenic catecholamines are adrenaline (epinephrine), noradrenaline (norepinephrine), dopamine and L-DOPA.

►Adrenaline
►Dopamine
►Noradrenaline

Catechol-O-methyl Transferase (COMT)

Definition

An enzyme that breaks down levodopa. Inhibitors of COMT prolong the duration of action of levodopa, thus alleviating end-of-dose wearing off.

Categorization

Definition

The recognition of different entities as members of the same group (category) based on some internal representation.

►Cognitive Elements in Animal Behavior
►Sensory Plasticity and Perceptual Learning

Category Learning/Memory

Definition

Category learning (or categorization) refers to the process of assigning an object to a concept. A concept is the set of properties that we associate with a particular class. To categorize an object appropriately, we need to have the prototype of the concept, which is one set of properties that describe the best examples of the concept. The prototype of the concept can also be established by learning.

►Learning

Category-specific Naming Deficits

Definition

Naming difficulty for words in specific semantic categories. Cases with herpes simplex virus encephalitis (HSVE or HSE) and degenerative diseases like Alzheimer's disease often reveal semantic memory loss for specific semantic categories. In HSVE, for instance, semantic memory loss for animates (mainly animals) is more striking than that for inanimate objects (e.g. hammer, scissors). Since picture or object naming is a serial process including activation of semantics and then retrieval of word phonology in the mental lexicon, naming reflects characteristics of this particular semantic memory loss, i.e. category-specific naming deficits.

►Alzheimer's Disease
►Verbal Memory

Cathodic Stimulation

Definition
Electrical stimulation of a structure performed by placing the negative pole of the stimulator over the structure itself.

Cauchy Stress

Definition
The flux tensor corresponding to the flux of linear momentum (i.e. the surface traction) in the Eulerian formulation.

►Mechanics

Cauchy's Theorem

Definition
If the flux of a physical quantity governed by a standard form of the balance law is assumed to depend on the boundary only through its local normal vector, then this dependence is actually linear. As a consequence of this important theorem, all fluxes are governed by linear operators (vectors and tensors).

►Mechanics

Cauda Equina (Filia Radicularia)

Synonyms
Cauda equina (filia radicularia)

Definition
The spinal cord extends from the brain down through the spinal canal inside the vertebral column. The spinal cord ends near the first lumbar vertebra in the lower back, forming the conus medullaris. The fibrous extension of the spinal cord is the filum terminale. The ventral and dorsal spinal nerves of the lumbar and sacral cord course in the shape of a horse's tail, parallel to the filum terminale, through the lumbar and sacral portion of the spinal canal to their respective exit points.

►Medulla Spinalis

Caudal

Definition
Towards the cauda (tail).

Caudal Ventrolateral Medulla (CVLM)

Definition
The CVLM is part of the ventrolateral medulla and located caudal to the rostral ventrolateral medulla. It contains inhibitory interneurons (e.g., involved in the baroreceptor reflexes to sympathetic cardiovascular neurons) and excitatory interneurons that mediate reflexes involving the rostroventrolateral medulla and peripheral sympathetic cardiovascular pathways.

►Autonomic Reflexes

Caudate Nucleus

Synonyms
Nucl. Caudatus; Caudate nucleus

Definition
The caudate nucleus and putamen together form the corpus striatum. Both are derived ontogenetically from the same anlagen, but are separated by incoming fibers from the internal capsule.

The corpus striatum is an important inhibitory component of motor movement programs and has manifold connections with the globus pallidus, substantia nigra and the motor cortex.

►Telencephalon

Caudate: Role in Eye Movements

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Definition

The caudate nucleus (CD) is a large structure in the basal ganglia and, together with the putamen, is called the striatum or the dorsal striatum. Its contribution to eye movements is mentioned in the section ►Basal ganglia – Role in eye movements.

Characteristics

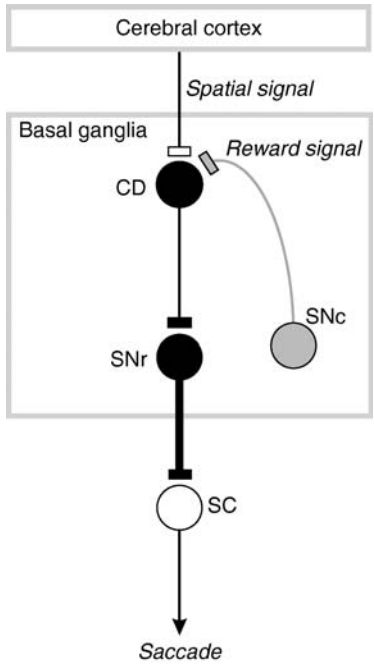
Higher Level Structures

A majority of inputs to the basal ganglia is destined to the striatum (CD and putamen); the striatum acts as the input station of the basal ganglia. After being processed in the striatum, signals are sent to other nuclei in the basal ganglia, substantia nigra (SN) and ►globus pallidus (GP). The final outputs of the basal ganglia are issued from part of the SN, which is pars reticulata (SNr), and part of the GP, which is the internal segment. The neural circuit in the basal ganglia related to eye movements originates in the CD and converges on the SNr, which then projects to the ►superior colliculus (SC) [1] (Fig. 1).

Lower Level Components

The saccade-related region in the CD roughly corresponds to the area that receives inputs from the ►frontal eye field (FEF) and ►supplementary eye field (SEF) [2]. It is therefore likely that the CD receives saccade-related signals from these cortical eye fields. However, inputs to the CD are only loosely segregated. That is, the saccade-related region in the CD receives inputs from other cortical areas including the ►dorsolateral prefrontal cortex. In addition to these converging inputs, the entire CD (together with the putamen and the ventral striatum) receives diffuse inputs from dopaminergic neurons in the substantia nigra pars compacta (SNc) and its surrounding regions [3]. It is likely that particular combinations of these inputs create signals unique to CD neurons.

A majority of neurons comprising the CD are called medium-spiny neurons: neurons with medium-sized cell bodies and many dendrites thickly covered with spines. They are the projection neurons: neurons that project axons to the outside of the CD. They are GABAergic and inhibitory. The projection neurons are highly hyperpolarized in the resting state and emit action potentials only occasionally. A minority of neurons (less than 5%) in the CD consist of several types of interneurons. One conspicuous type is the cholinergic interneuron, which is characterized anatomically as a large-aspiny neuron. They fire tonically and irregularly and are often called "tonically active neurons" or "TANs" [4].



Caudate: Role in Eye Movements.
Figure 1 Information processing in the caudate nucleus (CD) for the control of saccadic eye movement. *CD*, caudate nucleus; *SNr*, substantia nigra pars reticulata; *SC*, superior colliculus; *SNc*, substantia nigra pars compacta. Excitatory and inhibitory neurons and synapses are indicated by open and filled symbols, respectively. Gray symbol indicates a dopaminergic neuron which exerts modulatory effects on CD neurons. The thickness of the line (axon) roughly indicates the level of spontaneous activity. CD neurons receive spatial signals from the saccade-related areas in the cerebral cortex and reward-related signals from dopaminergic neurons in the SNc.

Higher Level Processes

Single unit studies using monkeys trained on saccade tasks have revealed that many CD projection neurons are clearly related to ►saccadic eye movements. Some of them respond to visual stimuli that potentially induce saccades to them. Other neurons become active before saccades. These visual-saccadic neurons have response fields which are usually centered in the contralateral field. The responses are often highly dependent on the context. Visual responses may be enhanced if the animal attends to or memorizes the stimulus. Saccadic activity may be present only when the saccade is guided by memory, or only when it is guided by visual stimuli. The neurons usually do not fire in relation to ►spontaneous saccades. Intermingled with such visual-saccadic neurons are

found more complex neurons, such as those related to expectation of task-specific events or ►reward. Such a complex nature of CD projection neurons appears to reflect the convergent inputs from the cortical eye fields (FEF and SEF) and from the dorsolateral prefrontal cortex.

Lower Level Processes

Studies suggest that these saccade-related neurons in the CD neurons control saccadic motor outputs by modifying neuronal activity in the SNr and the SC (Fig. 1) (see the section ►Substantia nigra – Role in eye movements). Electrical stimulation in the CD saccade-related region may elicit saccadic movements of the eye and the head to contralateral directions. If the electrical stimulation is short and weak, no movements are evoked, but it induces inhibitions and sometimes facilitations in SNr neurons. The former is likely to be mediated by the direct CD-SNr inhibitory connection, while the latter is likely to be mediated by the indirect pathway through the GP. Unlike CD projection neurons, SNr neurons are very active spontaneously, usually firing at more than 50 Hz. During the saccade tasks, many SNr neurons exhibit visual, saccadic, and memory-related activities, similarly to CD projection neurons. However, these activities usually show up as decreases in firing rates, unlike CD projection neurons. Since SNr neurons, especially those exhibiting saccade-related activity, have inhibitory connections to neurons in the SC, the decrease in SNr neuronal firing should lead to a disinhibition of SC neurons which control saccades to contralateral directions. In short, saccade-related activities in CD projection neurons would usually lead to facilitation of saccades to the contralateral directions. Note, however, the role of the CD on saccades may sometimes be suppressive, since some SNr neurons increase firing rates in relation to saccades presumably through the indirect pathways.

Recent studies have revealed another striking feature of CD neurons: Relation to reward-oriented behavior. Here, the amount of reward is biased depending on the direction of saccade: for example, rightward saccades are followed by a big reward and leftward saccades are followed by a small reward. This task has a strong behavioral impact: the saccade to the position associated with big reward is faster and earlier than that associated with small reward. The visual response of CD projection neurons is greatly enhanced and diminished if the saccade to the visual stimulus is expected to be followed by a bigger and smaller reward, respectively [5]. A minority of neurons exhibit the opposite reward modulation. The modulation is very common among visually responsive CD neurons (about 80%), and is often very strong such that the original directional tuning can be completed reversed. Similar reward-dependent modulation occurs for saccadic activity.

The relation of the CD to reward-oriented behavior is highlighted by a conspicuous group of CD projection neurons which cannot be classified as simply related to visual-saccadic processes [6]. They exhibit growing activity while the animal is waiting for the go-signal for a saccade. It appears to be related to saccade preparation. However, the activity occurs before instruction is given to which position the saccade should be made. The activity is nonetheless spatially selective in that it is present only when saccades to a contralateral, rather than ipsilateral, position are followed by a big reward. If there is no positional bias in reward, the anticipatory activity is much weaker.

Further studies suggest that the reward-position-sensitive anticipatory activity is transmitted to the SC through the SNr. Suppose a bigger reward is associated with saccades to a right target than a left target, CD neurons on the left side would exhibit stronger anticipatory activity than those on the right side (according to the findings described above). Since a major effect of CD neurons on SNr neurons is inhibitory, SNr neurons on the left side would exhibit a stronger decrease in firing rates than those on the right side. This is actually observed experimentally [7]. Since SNr neurons in turn inhibit SC neurons, the excitability of SC neurons on the left side would be elevated compared with those on the right side. This has also been confirmed experimentally [8]. There is now a clear imbalance in excitability between the two sides of the SC: Neurons in the left SC are more excitable than neurons in the right SC. This occurs before any instruction is given and far before a saccade is executed. This is an internal process based on the knowledge of the positional difference in reward amount. Under such a biased condition, a target that appears on the right side (i.e., associated with a big reward), which activates neurons on the left SC, would trigger a saccade more easily and more quickly than a target on the left side. In other words, the animal would make saccades more quickly to a more highly rewarded position. Such a behavioral bias is consistently observed experimentally. These results suggest that the CD is a critical brain area for reward-oriented motivational behavior.

Process Regulation

Such strong reward-dependent modulation of CD neurons may be caused by dopaminergic inputs (Fig. 1). As mentioned above, CD projection neurons have dendrites with many spines on which both axons from cortical neurons and axons from midbrain dopaminergic neurons make synapses. A majority of cortical axons originate from the cortical eye fields and are therefore likely to carry spatial signals. In contrast, midbrain dopaminergic neurons are known to carry reward-related signals, but not spatial signals [9]. They respond to reward which is given unexpectedly or, if

reward is expected, to a sensory stimulus that predicts the reward. In the reward-biased saccade task, dopaminergic neurons respond by excitation and inhibition to sensory stimuli that predict a reward that is larger and smaller than what is expected, respectively.

How could dopamine influence activity of CD projection neurons? Dopamine does not exert fast excitatory or inhibitory actions, but is thought to modulate other synaptic inputs, especially glutamatergic inputs from the cerebral cortex. These findings led to the following hypothesis: the spatial signals from the cortical eye field are enhanced if dopaminergic inputs are increased (i.e., a bigger reward is expected) and depressed if dopaminergic inputs are decreased (i.e., a smaller reward is expected). The interaction may occur within individual ►dendritic spines. This interaction may be due to the interactions among different ionic conductances. Or, it may be due to ►long-term potentiation (LTP) or depression (LTD). Recent studies have indicated that LTP indeed occurs if cortical inputs come in simultaneously with dopaminergic inputs and if the CD neuron fires [10]. In support of this hypothesis, the reward-dependent bias in saccades is reduced if dopaminergic transmission in the CD is blocked by injecting ►dopamine D1 antagonist [11].

The role of interneuronal processing in the CD is less clear. TANs, which are thought to be cholinergic, respond to reward or reward predictor, similarly to dopaminergic neurons, but also respond to a sensory stimulus that predicts the absence of reward or punishment. It has been suggested that cholinergic interneurons indicate that the reward is not equal among actions to choose, but do not indicate which action is the best or the worst. The latter function would be carried out by dopaminergic neurons. Cholinergic interneurons might detect the condition in which rewards are unequal and guide dopaminergic neurons to fully operate. However, this hypothesis needs to be examined in future experiments.

Pathology

The role of the CD in eye movements is usually not emphasized in clinical literature. However, patients with degenerative diseases involving the CD, such as Parkinson's disease and Huntington's disease, may exhibit severe difficulty in making eye movements [1]. The deficits may be more evident when the patients are asked to make eye movements voluntarily or based on memory; the deficits are less clear or absent when eye movements are made to visible targets. Local deprivation of dopaminergic innervation in the CD in monkeys leads to the severe paucity of spontaneous saccades and deficits in ►memory-guided saccades to the side contralateral to the denervation. However, eye movement deficit after a lesion in the CD is not a universal finding. This may partly be due to the anatomical configuration of the eye movement-related region in the CD. In monkeys trained on saccade tasks, many saccade-related neurons are found distributed in an anterior-posteriorly elongated zone in the CD excluding the most anterior part. A small lesion in the CD may not seriously disrupt information processing for saccadic eye movement.

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Causal Closure of the Physical

Definition

That the physical is causally closed means that every physical occurrence (which has a sufficient cause at all) has a sufficient totally physical cause. Usually, the causal closure of the physical is understood to allow that physical events have non-physical causes, too, and to deny only that non-physical causes are necessary.

Hence, if one traces the causal ancestry of a physical event, one never needs to leave the physical domain. If the physical is causally closed, there must be some true physical theory capable of exhaustively explaining why physical processes unfold in precisely the way they do (modulo, perhaps, quantum indeterminacies).

►Emergence
►Epiphenomenalism

Causal Theories of Knowledge

Definition

According to these theories, the true belief that p has to have an appropriate causal connection to the fact that p in order to count as knowledge.

►Knowledge

Causalgia

Definition

Causalgia is also called ►Complex Regional Pain Syndrome Type II (CRPS II) and develops after major peripheral nerve injury.

►Complex Regional Pain Syndromes – Pathophysiological Mechanisms

Causality

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Definitions

For the purpose of this essay, ►causality can be regarded as a relation between individual events, one event e_1 causing another event e_2. If one conceives causality in that way, one is well advised to adopt a fine-grained conception of events: an event is the instantiation (i.e. the occurrence) of a property by an object at a time.

Neuroscientific research seeks to provide us with some insight into the way in which the mind works. The problem of causality is the question how to account for causal relations that involve mental events (►Causality, mental), in particular mental events that cause physical events. In this context, "physical events" is to be understood in a broad sense, including chemical, biological, and neurophysiological events. There are causal chains that involve both physical and mental events. For instance, Mary's headache at noon today is a mental event. That mental event causes a chain of physical events that includes her lifting her right arm, her grasping an aspirin and her swallowing the aspirin. That latter event, in turn, causes her headache to vanish.

But how is it possible that mental events have physical effects? Consider the following four principles:

1. *Non-identity*: Mental evens are not identical with physical events. Mental events are instantiations of properties that involve consciousness (what it is like to, e.g., have a headache) or intentionality (that is, they represent something, being about something). These traits seem to draw a line of distinction between mental and physical events.
2. *Mental* ►*causation*: Mental events cause physical events. It is an essential part of our self-conception as human beings that our beliefs and desires cause a good deal of our behavior. It is a common and successful practice to explain the behavior of a person by referring to her beliefs and desires. Behavior – such as raising one's arm – includes changes on the microphysical level.
3. *Completeness*: For any physical event *p*, insofar as *p* has a cause, it has a complete physical cause. The search for an explanation of any physical event never takes us outside the physical domain (►Completeness of the physical domain). The laws of physics do not contain any gaps that would allow mental variables to make a causal contribution to physical events that is not made by physical variables. If we go down to fundamental physics, all events on the microphysical level have their probabilities completely determined by other microphysical events and microphysical laws.
4. *No systematic overdetermination*: If mental events cause physical events, there is no systematic overdetermination of the physical events in question by complete physical causes and additional mental causes.

From (1) to (4) follows what is known as the exclusion problem of mental causality: physical events seem to exclude – or at least to pre-empt – any causal efficiency of mental events. The problem is that each of the principles (1) to (4) is plausible if taken on its own. Any three of these principles are consistent, but the

conjunction of the four is not. In order to solve the problem of mental causality, one has to abandon – or at least to modify – one or more of these principles.

Description of the Theory

Theories of Causality

The main line of division in the metaphysics of causality is the one between Humean and anti-Humean theories. According to the Humean theories, causality is not a fundamental feature of the world. The causal relations that obtain between events in the world supervene on the distribution of the basic fundamental physical properties in space-time as a whole. These properties are not causal properties: they are purely qualitative, categorical properties. What they are (their essence) does not include any dispositions or causal powers. In short, the properties are not causal in themselves. Causality consists in relations of regular co-occurrence or counterfactual dependence between events that obtain against the background of the whole distribution of the fundamental, non-causal properties in space-time. Consequently, since that distribution is contingent, the relations of causality – and the laws that obtain in the world – are contingent, too [1].

The transference theory of causation [2] goes beyond Humeanism in conceiving causation as a physical process, namely as the transfer or exchange of a conserved physical quantity such as energy. This theory contradicts Humeanism in conceiving causality as a relation between two events that depends only on the space-time region in which these events are localized instead of supervening on the distribution of the physical properties as a whole. However, it remains neutral on the central issue as to whether the physical properties are causal in themselves or categorical. Consequently, it leaves open whether the causal link between two events is a contingent or a necessary one. As regards mental causality, in tying causality to physical processes, this theory can admit mental causality only on the assumption that mental events are identical with physical events, that is, only by rejecting principle (i).

According to anti-Humean theories, causality cannot be reduced to relations of regular co-occurrence or counterfactual dependence among events against the background of the whole distribution of the fundamental physical properties. There is causality in the production sense, that is, in the sense of one event bringing other events into existence in virtue of its properties. Consequently, the properties are themselves causal instead of being purely qualitative, categorical [3]: insofar as properties are certain qualities, they are powers to produce certain specific effects. Take charge as an illustrative example: insofar as charge is a qualitative property, distinct from e.g. mass, it is the power to build up an electromagnetic field, resulting in the attraction of opposite-charged and the repulsion of like-charged objects. Consequently, the causal relations that obtain between events in the world amount to necessary connections among those events, resulting from the powers that are the essence of the properties that the events that are causes instantiate. By the same token, the laws of nature are metaphysically necessary, being determined by the powers that are the essence of the properties instantiated in the world. For instance, in any possible world in which charge is instantiated, the occurrences of charge build up an electromagnetic field, resulting in the attraction of opposite-charged and the repulsion of like-charged objects.

The exclusion problem of mental causality is largely independent of the stance that one takes in the metaphysics of causality: even if one favors a Humean theory of causality, causality is tied to laws (laws of regular co-occurrence of events of the same types, or laws that are central to fixing the truth-values of the counterfactuals expressing causal relations). The physical laws prevail in any case, since the laws of the special sciences including psychology are always ceteris paribus laws, whereas the physical laws are strict laws (or at least stricter laws than the ones of the special sciences). Nonetheless, the metaphysics of causality has a bearing on mental causality: arguably only an anti-Humean theory of causation that recognizes causal properties (causal powers) can do justice to our experience of agency, that is, our experience of acting beings in the physical world [4].

Interactionistic Dualism

Since the conjunction of the four above-mentioned principles is not consistent, there are exactly four types of solution to the exclusion problem of mental causality, consisting in abandoning or modifying one of the four principles. If one maintains that mental events are not physical events (i) and if mental events cause physical events (ii), whilst physical events are not systematically causally overdetermined (iv), then one is committed to rejecting principle (iii), the causal completeness of the physical domain. The result is a dualistic metaphysics according to which mental and physical events constitute two different realms of being that causally interact with one another.

However, abandoning principle (iii) runs into a dilemma. The one horn of the dilemma is the conclusion that the laws of physics are false, because they do not indicate the correct probabilities for the occurrence of certain physical events in the brain. Even if we go down to the level of quantum physics and admit that the laws of quantum physics are irreducibly probabilistic, a problem occurs. If mental events are to count among the causes of some (quantum) physical events, they are thereby considered as raising the probabilities for the

occurrence of certain (quantum) physical events in the brain. Whenever a person has the intention to lift her left arm, the intention, being a mental cause, makes the occurrence of certain (quantum) physical events in her brain that are necessary for her arm going up much more probable than in the case where the person does not have that intention. Consequently, the laws of (quantum) physics must be taken to be false, for they do not yield the correct probabilities for the occurrence of certain (quantum) physical events in the brain, due to the presence of a further, mental variable. If one wishes to avoid this conclusion, one runs into the other horn of the dilemma, having to maintain that the laws of physics are not applicable to certain physical events: the brain has to be considered as not being a closed physical system, because it interacts with a mental system. Therefore, instead of the laws of physics, specific psycho-physical laws are necessary for neuroscientific research.

The general idea of interactionistic dualism implies that certain physical causal chains occurring in the brain contain gaps, and these gaps are filled by mental causes. However, neuroscientific research has not discovered any discontinuities within the causal chains that tie brain activities to bodily movements. For these reasons, interactionistic dualism is maintained only by a small minority of philosophers and scientists. The most detailed contemporary version of interactionistic dualism is due to the late neuroscientist John Eccles [5].

Epiphenomenalism

The fact that there are no gaps in the chains of physical causes that admit additional mental causes may be taken to cast doubt on the second principle (ii), claiming a causal efficacy of mental events. If mental events are distinct from physical events (i) and if there is a complete causal history of each physical event that contains only other physical events (iii) whilst systematic overdetermination is not admitted (iv), then the principle of mental causality has to go. The resulting position is ►epiphenomenalism: physical events determine mental events, whereas mental events, being distinct from physical events, do not determine anything. Hence, they neither cause other mental events nor physical events. However, epiphenomenalism simply abandons the view of ourselves as acting beings in the world. It is therefore not pursued as a serious option in the literature.

Physicalism

A less radical position is the one that recognizes the causal efficacy of mental events, but seeks to accommodate mental causality within the scientific worldview, rejecting the principle of non-identity of mental and physical events (i). Mental events cause physical events, being identical with physical events. Consequently, the principle of mental causation does not clash with the principles of completeness (iii) and no systematic overdetermination (iv). More precisely, if events are conceived in a fine-grained manner as an object instantiating a property at a time and if all mental events are identical with physical events, then some physical events are mental events: insofar as they are instantiations of a mental property *M*, they are instantiations of a physical property *P*, so that what they cause qua being *P*, they cause qua being *M*.

One way to spell out physicalism is the type-type identity theory according to which every mental type is identical with a physical type. For instance, every pain event is identical with a neuronal event of the type *N*. It is the task of neuroscientific and psychological research to establish biconditional correlations between mental and physical types that license the inference to identity. The discovery of correlations is an empirical matter. The conclusion to identity between mental and physical types is a matter of philosophical argument. If mental types are identical with physical types, then the description of any mental type can be reduced to a physical description, although the meaning of the mental concepts can remain different from the meaning of the corresponding physical concepts. In the same way, if water is H_2O, then the description of water can be reduced to the chemistry of H_2O, although the meaning of the concept "water" is different from the meaning of the concept "H_2O." Therefore, the type-type identity theory is a reductive ►physicalism.

The classical objection against the type-type identity theory is based on the notion of the ►multiple realization of mental types. This objection claims that one and the same mental type can be realized in different physical ways so that the mental type is not identical with any single physical type. For instance, pain may be identical with neural events of the type *N* in humans, but in octopuses, it is identical with brain events of another type. Furthermore, it seems in principle possible that even robots or extraterrestrial beings ("Martians") are in pain, although in that case pain would be realized in an entirely different physical way. Over and above this kind of multiple realizability limited to species, it has been claimed that not even within a species, or even within a single individual, a given mental type is always realized by tokens of the same physical type. Mental events of the type "desiring an ice-cream" may be realized in different ways in a single individual throughout time.

However, type-identity is not necessary to solve the problem of mental causality within the framework of physicalism. Token identity is sufficient: for mental events to be causally efficacious given completeness (iii) and no systematic overdetermination (iv), it is sufficient that for each single event insofar as it is *M*, it is identical with a *P*, but no identity of the property

types M and P is necessary. In that vein, retreating to token identity is the common reply to the argument from multiple realizability, and ▶functionalism is the most common way to spell out token identity in the mentioned fine-grained sense. According to functionalism, a type of mental events M is defined by the characteristic causes and effects that events of the type M have. Each event of the type M is realized in a physical way – that is, by a configuration of physical events that satisfies the functional definition of M –, but there is no unique physical way in which every event of the type M is realized. In that sense, mainstream functionalism considers itself as a non-reductive physicalism [6].

Nonetheless, functionalism faces a problem as has become clear since the nineties: insofar as mental types are not identical with physical types, they cannot be but epiphenomenal given completeness (iii) and no systematic overdetermination (iv). One may seek to avoid that problem by conceiving types not as anything ontological, but as concepts that we employ to classify the events in the world: property tokens that come under one and the same abstract mental concept "M" may come under different, more precise physical concepts "P_1," "P_2," "P_3," etc. However, the problem remains: if one maintains that the descriptions (theories, laws) in "M"-terms cannot be reduced to descriptions (theories, laws) in "P"-terms due to multiple realizability, it is unclear how non-reducible mental concepts, laws or theories can possess a scientific quality: as a consequence of (iii), there is a complete physical description of every event possible that fully explains the event in question.

Due to the mentioned problems, a reductive physicalism within the framework of a functional conception of mental events has become one of the central topics of the current discussion [7]: if one accepts completeness (iii) and no systematic overdetermination (iv), then it seems that in order to vindicate the causal efficacy of mental events, one is committed to token identity in the mentioned fine-grained sense; and in order vindicate the scientific quality of the descriptions, laws and theories that use mental concepts, one is committed to the possibility of reducing the mental descriptions (laws, theories) to physical descriptions (laws, theories). Against that background, it seems furthermore that multiple realizability does not necessarily imply non-reductionism: one can avoid the anti-reductionist consequences of multiple realizability by conceiving more fine-grained mental sub-types that are finally coextensive with the physical realizer-types [8].

In any case, even if these issues are cleared, the main question remains whether the characteristic features of mental events (consciousness, intentionality) can be understood within the conceptual framework of physicalism and functionalism: as regards consciousness, the question is whether the phenomenal character of experience (what it is like to be …) can be conceived in a functional manner. As regards intentionality, the question is whether conceptual content can be conceived in terms of causal roles that are internal to the person or her brain or whether there is a constitutive dependence of conceptual content on external factors such as the social environment. In the latter case, two persons can be indistinguishable as regards the physical properties of their brains, but distinct as regards the conceptual content that their mental events instantiate.

Overdeterminationism

Finally, one can call into question the rejection of systematic overdetermination (iv), making use of the possibility to postulate some sort of overdetermination in order to retain mental causality together with the principles of completeness (iii) and non-identity (i). By formulating a test for overdetermination based on certain counterfactual conditionals, it can be shown that the way mental events overdetermine physical effects is disanalogous to that found in paradigm cases of overdetermination, such as the victim being killed by two fatal shots in the heart at the same time [9]. This disanalogy ultimately results from the fact that mental causes, even if non-identical to physical causes, are still taken to stand to these causes in a metaphysical determination relation, namely strong supervenience, and from the fact that they are spatiotemporally coincident with the physical causes. At least under the counterfactual criteria for causality, many mental events can then be shown to satisfy all conditions that are necessary and sufficient for causality without being identical to physical events ([10], Chap. 4).

However, by tying the mental causes to physical causes through strong supervenience in order to avoid the stock objections against the idea of systematic overdetermination, this solution implies that for one event to supervene strongly on another event with which it is not identical is a sufficient condition for the supervenient event systematically overdetermining the effects that the subvenient event causes. Furthermore, one can object that it is possible to show that in the typical situations, the physical cause satisfies still stronger counterfactual criteria with respect to the effect than does the mental cause. It seems therefore possible that, in the end, this asymmetry will imply an epiphenomenality of mental events after all.

Nonetheless, the overdetermination solution has long been neglected in the literature, but today, it stands together with the renewed interest in reductive physicalism at the centre of the discussion: if one is not prepared to endorse token identity of mental and physical events in the mentioned fine-grained sense, trying to make a case for some sort of systematic overdetermination seems to be the only other reasonable option.

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Causality, Mental

Definition

Mental events are causally efficacious: they bring about other mental events as well as physical events.

►Causality

Causation

Definition

►Causality

(CBAxC57BL/6)F1

Definition

The hybrids of one generation of mice of lines CBA and C57Bl/6.

CCK

Definition

►Cholecystokinin

CD8

Definition

T cells express either CD4 or CD8 molecules on their cell surface. While CD4 is expressed on helper T cells, CD8 molecules are expressed on cytotoxic T cells, and interacts with major histocompatibility complex (MHC) I molecules. CD8 belongs to the immunoglobulin superfamily.

CD14

Definition

Cell surface molecule that functions as a receptor for lipopolysaccaride.

CD120

►Brain Inflammation: Tumor Necrosis Factor Receptors in Mouse Brain Inflammatory Responses

Cdc42

Definition

A member of the Rho-family of GTPases that regulates several aspects of cell function by definition controlling cytoskeletal changes. The activities of Rho-family GTPases are highly regulated and their cytoskeletal changes are one of the basic mechanisms involved in controlling cellular size, shape, and motility.

Cell Adhesion Molecules

Definition

A diverse family of cell surface molecules, such as neural cell adhesion molecules (N-CAM), which allow cell–cell and cell–extracellular matrix adhesion, recognition, activation, and migration.

Cell Autonomy

Definition

Description of the source of a signal with respect to the cell the signal acts upon. Cell autonomous means a cell produces its own signal, whereas a signal-independent of the receiving cell functions in a cell non-autonomous fashion.

Cell Cycle

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Synonyms

Cell cycling

Definition

The "cell cycle" is defined as the process by which a single cell divides into two daughter cells. This essay will discuss somatic cell division or somatic mitosis, i.e. the process during which a single diploid cell divides into two diploid cells, in the context of the ontogeny of the central nervous system in mammals. The focus will be on the regulatory mechanisms of cell cycles of neural progenitor cells that generate the projection neurons of the neocortex. The emphasis is on the G1 phase regulation of neural progenitor cells and the regulatory mechanisms embedded in the G1 phase that ultimately determine the number of projection neurons and their distribution through the six-layered structure of the neocortex.

Characteristics

Phases of the Cell Cycle

A single cell division cycle has two major phases, namely the DNA synthesis (S) phase and the cell division or mitosis (M) phase. Between these two phases, there are two "gap" or "inter-" phases called gap 1 (G1) and gap 2 (G2) phases. There is another cell cycle state called the G0 phase, when cells remain resting but capable of reentering into a proliferative cell cycle. It is believed that in the developing brain most, if not all, newly developed neurons are not in the G0 state but in the terminally differentiated state. The G1 phase is initiated as M phase is completed and completed as S phase begins; the G2 phase is initiated as S phase is completed and completed as M phase begins. Dividing cells proceed through these four phases repeatedly. Thus, this continuing process is called the cell "cycle."

Among the four phases of the cell cycle, the G1 phase is considered to be a critical period when proliferative cells receive extracellular "cues" that may lead these cells to either proceed to S phase or to exit from the cycle. These extracellular cues include extrinsic molecules such as neurotrophic factors and mitogens/anti-mitogens of various kinds and environmental substances such as drugs and pollutants.

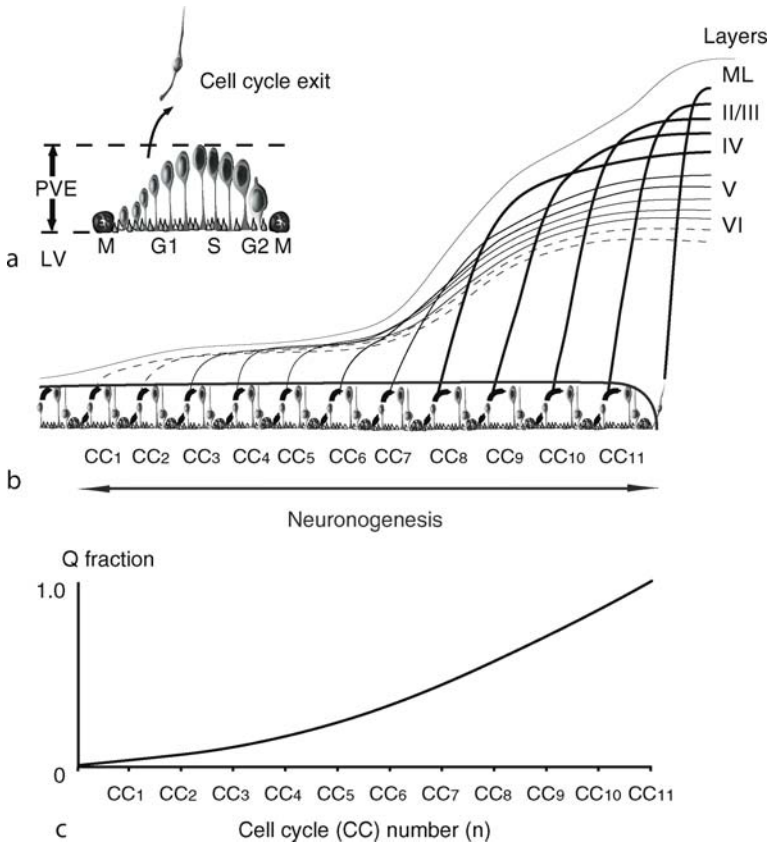
Length of the Cell Cycle

Generally, the total cell cycle length of undifferentiated progenitor cells varies greatly, not only among different types of tissues/organs to which these cells give rise but also among different time points during ontogeny of the tissue/organ. For example, while neural progenitor cells in the pseudostratified ventricular epitherium (PVE, Fig. 1a) lining the surface of the lateral ventricles of the mouse embryonic forebrain take ~8 h to complete a single cell cycle on embryonic day 11 (E11), those on E16 take as long as 18 h (Fig. 2) [1].

In this respect, the observation that the major contributor to such cell cycle length alteration is the prolongation of G1 phase but of no other phases of the cell cycle is of critical biological significance; the length of the G1 phase increases systematically from 3.2 h to 12.4 h as neocortical histogenesis proceeds, whereas the lengths of G2, M and S phases remain unchanged or change only unsystematically (Fig. 2) [1].

Probability of Cell Cycle Exit

It is of note that G1 phase is the phase of the cell cycle when a given proliferative progenitor cell chooses whether to proceed to S phase and remain in the proliferative cell cycle or to leave the cycle and become terminally differentiated (Fig. 1a). In other words, for a single G1 phase progenitor, there are only two fates to follow (all-or-none kind of decision making) either to stay in or to exit the cycle [2]. Obviously, the population of neuronal progenitor cells is composed of numerous proliferative cells, which makes the population probability of cell cycle exit anywhere between 0% and



Cell Cycle. Figure 1 Overview of Critical Events of Neocortical Neuronogenesis. (a) Schematic representation of interkinetic nuclear migration. The position of cell nuclei of neuronal progenitor cells changes systematically as they proceed through cell cycle phases (M, G1, S, G2 *along the abscissa*). A fraction of cells exits the cycle during G1 phase (*upward arrow*). *PVE* pseudostratified ventricular neuroepitherium; *LV* lateral ventricle. (b) The founder population of neural progenitors and their progenies execute 11 cell cycles (CC_1-CC_{11}) over the neuronogenetic interval. The early-formed neurons are destined for the deepest cortical layers (*dotted curved lines* connecting the PVE and layers VI), whereas the later formed neurons are destined for the more superficial layers (*solid curved lines* connecting the PVE and layers IV and II/III). (c) The fraction of daughter cells that exits the cell cycle (Q fraction) increases slowly during the initial phase of neuronogenesis and then accelerates to reach the final value of 1.0 at the completion of neuronogenesis when 100% of progenitor cells leave the cycle.

100%. In the course of neocortical histogenesis, the probability of cell cycle exit or ▶quiescent (Q) fraction increases from 0 (i.e. 0%) at the outset to reach 1.0 (i.e. 100%) at the completion of the interval of neuron generation (i.e. neuronogenesis, Fig. 1c) [2].

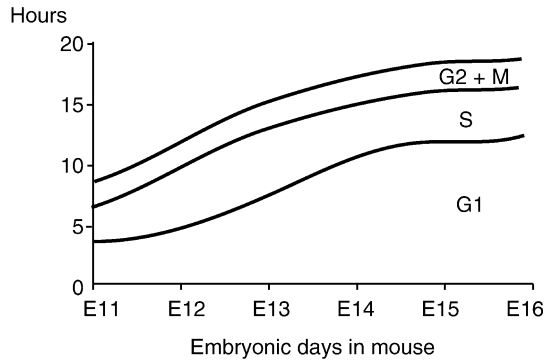
Structural Regulation

Interkinetic Nuclear Migration

The position of the cell nuclei of neural progenitor cells changes systematically as they proceed through cell cycle phases. This phenomenon is called interkinetic nuclear migration (Fig. 1a). The nuclei of S phase cells are located within the outer half of the proliferative epithelium. This area is called the S phase zone. Nuclei of cells in S phase are readily recognized by S phase tracers such as BrdU. Those nuclei then in the course of G2 phase move "downward" to the lateral ventricle to execute mitotic process (M phase) at the surface of the lateral ventricle. Nuclei of neural progenitor cells in G1 phase move "upward" towards the S phase zone.

Cell Cycle Sequence and Layer Composition

It has long been known that the early-formed neurons are distributed in the deeper layers of the neocortex, while the later formed neurons are distributed in the superficial layers (inside-out pattern neuronogenesis). Investigations in mice revealed that the cell cycle of origin is the strong determinant of the layer distribution of projection neurons arising from that cell cycle (Fig. 1b) [3].



Cell Cycle. Figure 2 Lengths of cell cycle phases. The major contributor to cell cycle lengthening during neuronogenesis is the prolongation of the G1 phase but of no other phases of the cell cycle.

Process Regulation

Molecules that Control Cell Cycle Progression

Cyclins and Cyclin Dependent Kinases

Progression through cell cycle phases is strongly governed and precisely regulated by a set of proteins called ►cyclins and cyclin dependent kinases (►CDKs). Cyclins and CDKs act as accelerators of the progression of cell cycles i.e. CDKs phosphorylate substrates in the presence of cyclins, phosphorylation of key molecules is critical to trigger entry into the next phase of the cell cycle. Cyclin molecules have been named after their expression pattern during a single cell cycle; expression increases and then decreases in a cell cycle-phase specific manner. For example, cyclin D1 expression level increases in the course of G1 phase and decreases before initiation of S phase. The kinase activity of CDKs is also known to be augmented by cyclin activating kinases (CAK) [4].

There are eight cyclins and nine CDKs reported to date. These cyclins and their specific partner CDKs working together serve to promote cell cycle progression, particularly at the passage through the corresponding ►restriction point (see "Function" for details).

There are many target substrates of cyclin/CDK complexes. In G1 phase progression, cyclin Ds/CDK4/6 and cyclin E/CDK2 are the critical sets of molecules to hyperphosphorylate retinoblastoma protein (Rb). Hyperphosphorylation of Rb releases transcription factor E2F from Rb, which leads to E2F dependent transcription of target genes including cyclin E, which in turn is necessary for S phase progression [4].

CDK Inhibitors

There is a group of ►CDK inhibitors (CDKIs), which serve as negative regulators of cell cycle progression. CDKIs are divided into two groups, inhibitors of CDK4 (INK4) and CDK interacting (Cip) or kinase inhibitor proteins (Kip). INK4s include four proteins, p16INK4a, p15INK4b, p18INK4c and p19INK4d. Cip/Kip includes p21Cip1, p27Kip1 and p57Kip2 [4].

As is the case with cyclins/CDKs, each of the CDKIs has specific inhibitory activity and functions as a decelerator of cell cycle progression only upon specific pairs of cyclins/CDKs. INK4s in general bind to CDK4 and inhibit kinase activity; p27Kip1 specifically inhibits cyclin E/CDK2 kinase activity, which leads to inhibition of entry into S phase.

Given that anti-mitogenic factors serving as differentiation inducers induce some of the CDKIs including INK4s and Cip/Kip, it is thought that CDKIs promote cell cycle exit and hence cellular differentiation.

Function

The Restriction Point as a Critical Regulatory Checkpoint

There are some kinds of checkpoints called "restriction points" during cell cycles [5]. These "points" are actually short "intervals" embedded within each of G1, S, G2 and M phases, during which a sequence of critical events for proper cell cycle progression occurs [4]. They were first discovered by analysis of the cell cycles of yeast. For example, once a cell passes through the G1 restriction point, the cell is committed to enter S phase and duplicate DNA. Probably more precisely, unless the cascade of molecular events for G1 phase progression and for S phase re-entry has been duly completed, no cell is allowed to pass through the G1 restriction point [5] hence the word "restriction."

Critical Parameters for Neuron Production

Two parameters govern the proliferative behavior of the progenitor populations and thus determine the total number of neurons produced. These parameters are (i) the total number of cell cycles executed during the interval of neuronogenesis and (ii) the probability of cell cycle exit (►quiescent or Q fraction) i.e. the proportion of daughter cells that becomes permanently quiescent after cell division (Fig. 1c). The incidence of apoptotic cell death within the proliferative progenitor population is very small and is unlikely to be a major factor in determining the total number of neurons produced.

The number of cell cycles that constitute the neurogenetic interval has been estimated to be 11 in mice. The values of Q fraction have been directly measured by using two S phase tracers, BrdU and tritiated thymidine [6]. The Q fraction determined thus increased very slowly during the initial phase of neuronogenesis and then accelerated rapidly to reach the final value of 1.0 at the completion of neuronogenesis when 100% of progenitor cells have left the cycle (Fig. 1c).

Experimental over-expression of p27Kip1 protein, one of the CDKIs, has been shown to result in a premature increase in Q fraction, leading to a decreased number of projection neurons in the neocortex [7,8]. On the contrary, experimental deprivation of p27Kip1 resulted in abnormally low values of Q fraction in the early/middle phases followed by a "catch-up" increase in the late phase of neuronogenesis [9]. Such an altered pattern of Q fraction progression resulted in an increased number of projection neurons in the neocortex.

It has been inferred that both G1 phase length and Q fraction are coordinately regulated during G1 phase by common mechanisms that involve such molecules as cyclin/CDKs and CDKIs. Given that the cell cycle of origin (time of production) and the layer distribution of those neurons arising from that cell cycle are closely correlated, it may be concluded that such mechanisms governing G1 phase progression and cell cycle exit are also intimately involved in phenotype determination once out of the cell cycle.

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Cell Differentiation

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C

Definition

Differentiation is the process by which cells become more specialized and mature. In this process, neural stem cells become mature neurons or glial cells.

Characteristics

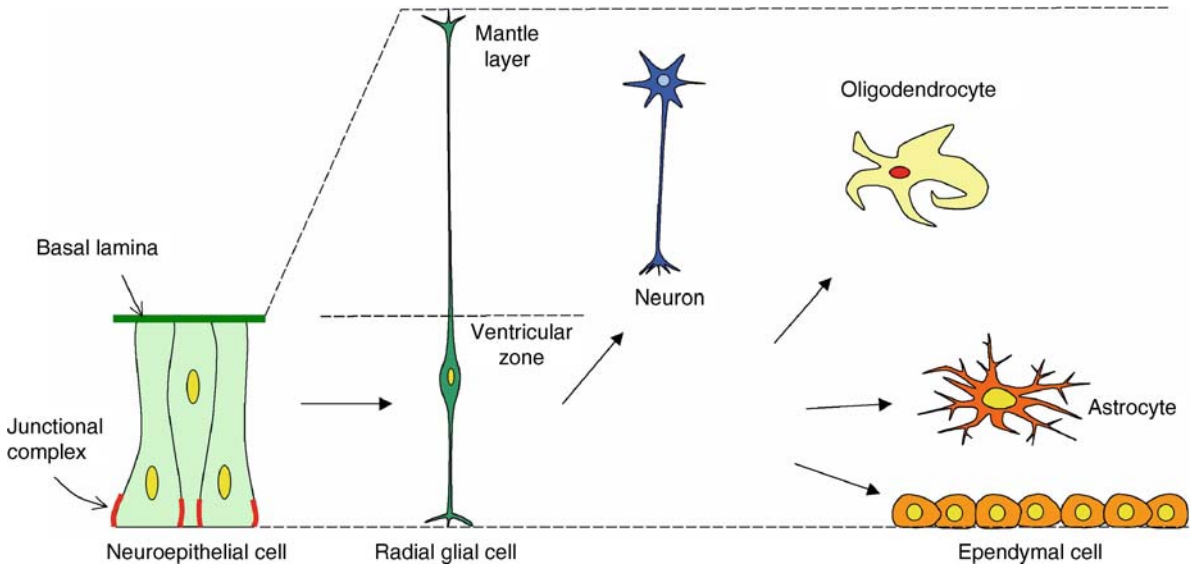
Description of the Process

In the developing central nervous system, multipotent neural stem cells progressively become mature neurons or glial cells. This process involves three steps, (i) fate determination, (ii) subtype selection and (iii) maturation. In the fate determination step, the ▶cell fate is determined; cells acquire a neuronal or glial ▶cell identity. During or subsequent to the fate determination step, neuronal and glial subtypes are selected. In the case of neurons, a subtype selection is made from many options, such as motor versus sensory subtypes and excitatory (glutamatergic) versus inhibitory (GABAergic) subtypes. For glial cells, selection for oligodendrocytes versus astrocytes is made. In most cases, the fate determination and subtype selection steps proceed at the same time. Each subtype of cells then becomes morphologically and functionally mature.

Higher Level Processes

The developing central nervous system initially consists of neuroepithelial cells, which have epithelial cell characteristics such as tight junctions and adherens junctions at the apical side and a basal lamina on the basal side (Fig. 1) [1,2].

Neuroepithelial cells are the first form of neural stem cells. These cells undergo self-renewal by symmetrical cell divisions but do not usually give rise to neurons. As development proceeds, neuroepithelial cells gradually change into radial glial cells, which have radial processes (radial fibers) reaching the ventricular (apical) and pial (basal) surfaces (Fig. 1) [1,2]. Radial glial cells were named thus because they were long thought of as specialized glia with radial fibers that guide neuronal migration. However, it was later found that they are the second form of neural stem cells. Radial glial cells undergo asymmetrical cell divisions in which one radial glial cell produces one radial glial cell and one neuron (or one neuroblast). Radial glial cells also undergo symmetrical cell divisions in which one radial glial cell



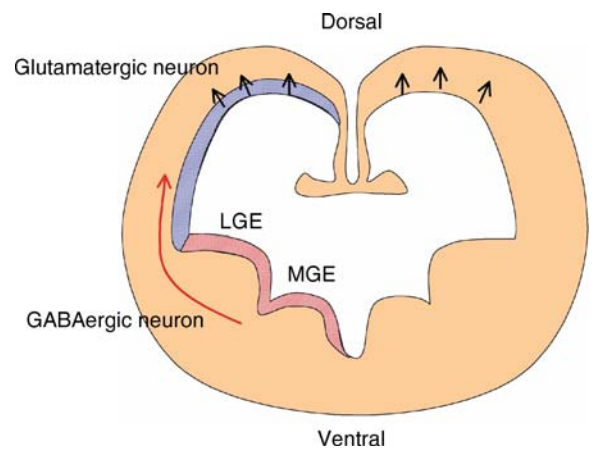
Cell Differentiation. Figure 1 The cell fate determination step. Neuroepithelial cells, the first form of neural stem cells, have epithelial cell characteristics such as the junctional complex at the apical side and the basal lamina on the basal side. These cells undergo symmetrical cell divisions and do not usually give rise to neurons. Neuroepithelial cells gradually change into the second type of neural stem cells, called radial glial cells. These cells undergo asymmetrical cell divisions and give rise first to neurons. After the production of neurons, radial glial cells give rise to oligodendrocytes, astrocytes and ependymal cells. Radial glial cells disappear after birth, but some astrocytes or astrocyte-like cells function as neural stem cells in the adult brain.

produces two neurons (or two neuroblasts). While the cell bodies of radial glial cells remain in the ventricular zone, neurons (or neuroblasts) migrate along the radial fibers to the outer layers. During migration, neuroblasts proliferate further to produce more post-mitotic neurons. These cells settle in the outer layer (mantle layer, cortical plate) and become mature neurons.

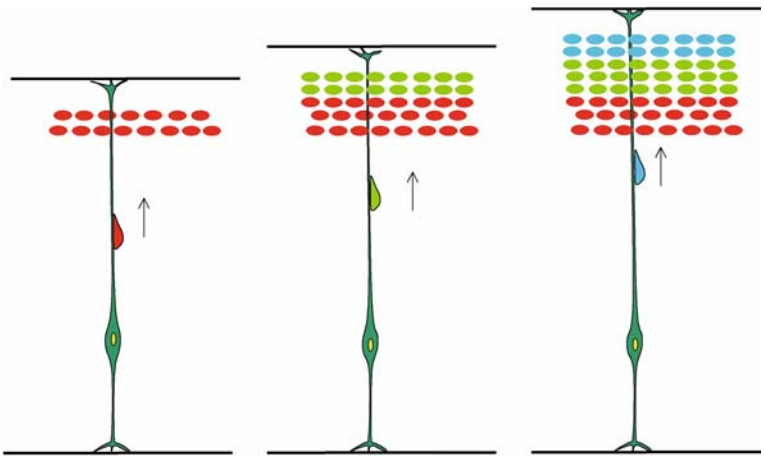
During or after neuronal fate determination, neuronal subtype selection is made. In the telencephalon, excitatory (glutamatergic) neurons are developed in the dorsal region, while inhibitory (GABAergic) neurons are developed in the ventral region (Fig. 2).

Excitatory neurons migrate radially inside the dorsal telencephalon while inhibitory neurons migrate tangentially from the ventral to the dorsal telencephalon. Thus, excitatory and inhibitory neurons in the dorsal telencephalon have different origins, indicating that subtype selection is controlled by spatial cues. In the dorsal telencephalon, early developed neurons form deep cortical layers while later developed neurons migrate through the early developed neurons towards the outer surface and form more superficial cortical layers (inside-out) (Fig. 3).

Different layers contain different subtypes of neurons. Early developed neurons in the deep layers (mainly, layer V) have projection efferents (projecting to the subcortical regions, brainstem and spinal cord), while late developed neurons in the superficial layers (layers II and III) have association efferents (projecting to the ipsilateral or contralateral cortex), indicating that cells with different times of development acquire different neuronal subtypes. Thus, neuronal subtype selection is controlled by temporal cues as well as by spatial cues. Neurons then



Cell Differentiation. Figure 2 Spatial control of the subtype selection step. In the telencephalon, excitatory (glutamatergic) neurons are developed in the dorsal region while inhibitory (GABAergic) neurons are developed in the ventral region. Excitatory neurons migrate radially inside the dorsal telencephalon while inhibitory neurons migrate tangentially from the ventral to the dorsal telencephalon. Thus, subtype selection is controlled spatially.



Cell Differentiation. Figure 3 Temporal control of the subtype selection step. Early developed neurons (*red*) form the deep cortical layers while later developed neurons (*green and blue*) migrate through the early developed neurons towards the outer surface and form the more superficial cortical layers (inside-out). Neurons in different layers acquire different properties. Thus, the subtype selection is controlled temporally.

become mature by extending axons and dendrites and forming synapses.

After production of neurons, radial glial cells give rise to glial cells (oligodendrocytes and astrocytes) (Fig. 1). Oligodendrocytes are developed in some restricted regions from early to late stages of neural development, while astrocytes are developed widely in the nervous system at the last stage. Radial glial cells also give rise to ependymal cells, the epithelial lining of the ventricles (Fig. 1). After birth, radial glial cells disappear, but neural stem cells remain in the adult brain and are morphologically similar to astrocytes at this stage. Active neurogenesis from such astrocyte-like adult neural stem cells occurs in the subventricular zone of the lateral ventricles and in the subgranular zone of the dentate gyrus.

Regulation of the Process

Regulation by Two Types of bHLH Genes

Cell differentiation involves fate determination, subtype selection and maturation steps, as described above. These steps are regulated by basic helix-loop-helix (bHLH) genes, which are classified into two types, activators and repressors [3–5]. Both types of bHLH factors form a dimer through the HLH domain and bind to DNA via the basic region. The activator-type bHLH factors such as Mash1, Math1 and Neurogenin form heterodimers with the ubiquitously expressed bHLH factor E47 and activate gene expression by binding to the E box (CANNTG) (Fig. 4a).

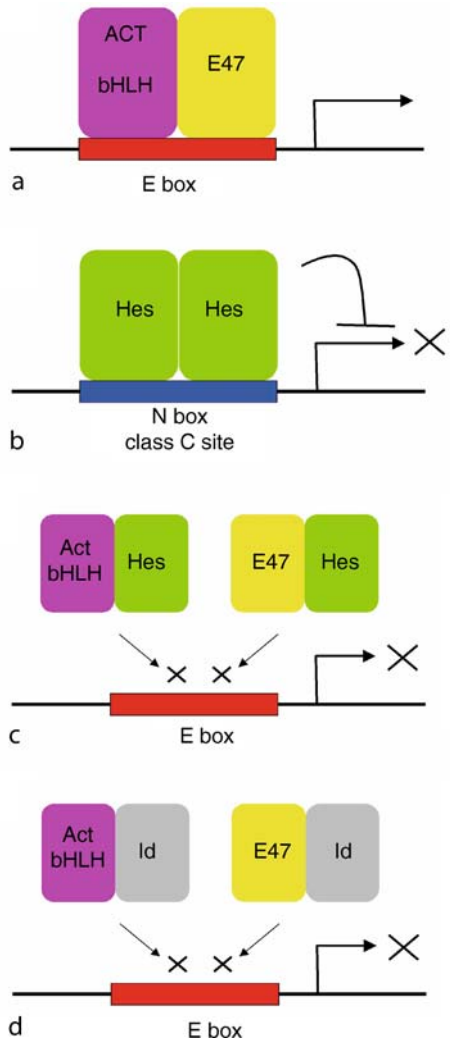
The repressor-type bHLH factors such as Hes1, Hes3 and Hes5 form homodimers and repress gene expression by binding to the N box (CACNAG) or the class C site (CACGCG) (Fig. 4b). The target genes for Hes factors include the activator-type bHLH genes such as *Mash1*. Hes1 also forms heterodimers with activator-type bHLH factors, but these heterodimers cannot bind to DNA (Fig. 4c). Thus, Hes1 inhibits both the expression and activities of the activator-type bHLH factors. Other factors, Id1, Id2 and Id3, which have an HLH domain but lack a basic region, cannot bind to DNA. Ids inhibit activator-type bHLH factors by forming non-DNA-binding heterodimers through the HLH domains (Fig. 4d).

Fate Determination by bHLH Genes

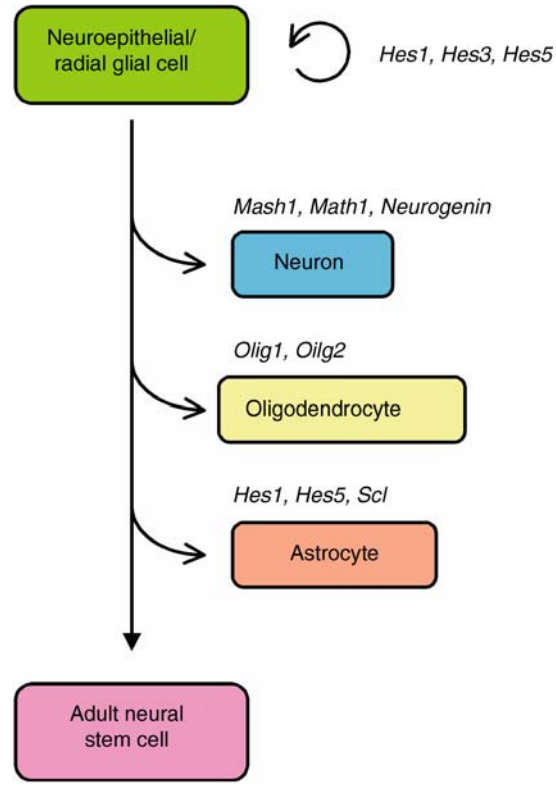
Maintenance of neural stem cells is regulated by repressor-type bHLH genes (Fig. 5). Misexpression of *Hes1*, *Hes3* or *Hes5* inhibits neuronal fate determination by repressing activator-type bHLH genes and maintains neural stem cells. Conversely, in the absence of *Hes* genes, neural stem cells prematurely differentiate into early-developing neurons at the expense of later developing cell types.

Neuronal fate determination is regulated by the activator-type bHLH genes such as *Mash1*, *Math* and *Neurogenin* (Fig. 5). Misexpression of *Mash1*, *Math* or *Neurogenin* induces neuronal fate determination, while in the absence of these genes glial fate determination is promoted [3–5]. The activator-type bHLH genes not only induce neuronal-specific gene expression, but also, inhibit glial-specific gene expression and suppress the neural stem cell state by inducing Hes6, an inhibitor for Hes1.

Glial fate determination is regulated by repressor-type bHLH genes. Oligodendrocyte formation is regulated by the repressor-type bHLH genes *Olig1* and *Olig2* and astrocyte formation is regulated by *Hes1* and *Hes5* (Fig. 5). It was recently shown that fate determination of subsets of astrocytes is also regulated



Cell Differentiation. Figure 4 Two types of bHLH factors. (a) The activator-type bHLH factors form heterodimers with the ubiquitously expressed bHLH factor E47 and activate gene expression by binding to the E box. (b) The repressor-type bHLH factors such as Hes1 form homodimers and repress gene expression by binding to the N box (CACNAG) or the class C site. (c, d) Both Hes and Id factors inhibit activator-type bHLH factors by forming non-DNA-binding heterodimers through the HLH domains.



Cell Differentiation. Figure 5 Regulation of cell fate determination by bHLH genes. Maintenance of neural stem cells is regulated by the repressor-type bHLH genes *Hes1*, *Hes3* and *Hes5*. Neuronal fate determination is regulated by the activator-type bHLH genes such as *Mash1*, *Math* and *Neurogenin*. Oligodendrocyte formation is regulated by the repressor-type bHLH genes *Olig1* and *Olig2*, while astrocyte formation is regulated by *Hes1*, *Hes5* and *Scl*.

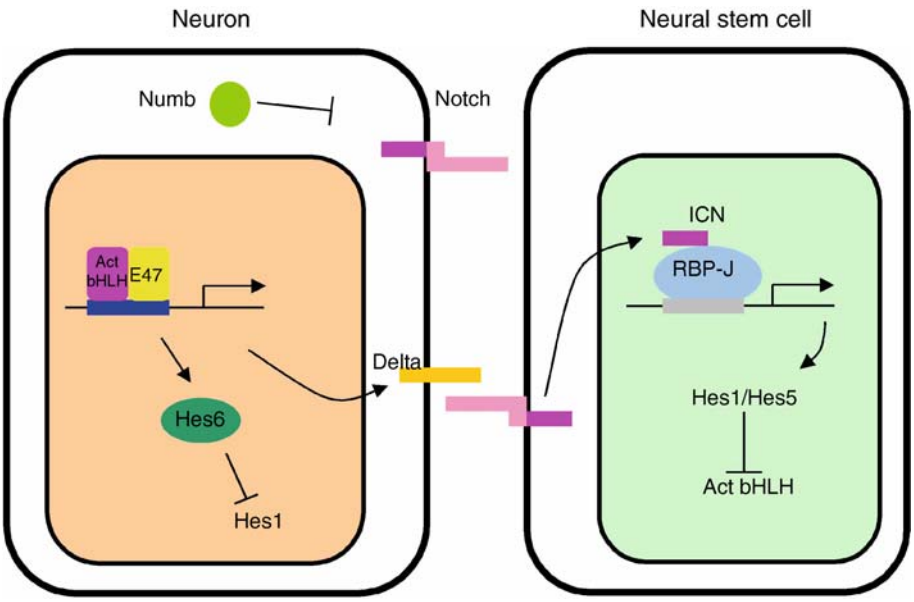
by the activator-type bHLH gene *Scl* [6] (Fig. 5). Thus, in glial development, both fate determination and subtype selection seem to be controlled at the same time.

Cross-Regulation of bHLH Genes and Notch Signaling

Hes1 and *Hes5* expression is regulated by Notch signaling [5]. Notch, a transmembrane protein, is activated by its ligands such as Delta. Upon activation by Delta, the intracellular domain of Notch (ICN) is cleaved and transported into the nucleus to form a complex with RBP-J (Fig. 6).

RBP-J alone represses *Hes1* and *Hes5* expression, but the ICN-RBP-J complex activates *Hes1* and *Hes5* expression. Thus, Notch activation leads to induction of *Hes1* and *Hes5*, which maintain neural stem cells by repressing the activator-type bHLH gene expression (Fig. 6). When neural stem cells undergo asymmetric cell division, Numb is asymmetrically distributed, yielding $Numb^{+}$ and $Numb^{-}$ cells (Fig. 7) [7,8].

Numb is known to inhibit Notch activity by interacting with its intracellular domain. Thus, in the $Numb^{+}$ cell, Notch signaling is suppressed, resulting in down-regulation of *Hes1* (Fig. 7) and *Hes5* and induction of activator-type bHLH genes (Fig. 6). The activator-type bHLH factors suppress residual Hes1/5 activities by inducing Hes6 and up-regulate expression of Delta, which activates Notch signaling of the neighboring cells (which are $Numb^{-}$ cells). As a result,



Cell Differentiation. Figure 6 Cross-regulation of bHLH genes and Notch signaling. During asymmetric cell divisions, Numb is asymmetrically distributed, resulting in Numb$^+$ and Numb$^-$ cells. In Numb$^+$ cells, Notch signaling is inactivated, resulting in down-regulation of *Hes1* and *Hes5* and induction of activator-type bHLH genes. The activator-type bHLH factors suppress residual Hes1/5 activities by inducing Hes6 and up-regulate expression of Delta, which activates Notch signaling of the neighboring Numb$^-$ cells. In Numb$^-$ cells, Notch is activated by Delta and the intracellular domain of Notch (ICN) is cleaved and transported into the nucleus to form a complex with RBP-J. The ICN-RBP-J complex induces expression of *Hes1* and *Hes5*, which inhibit activator-type bHLH factors. As a result, Numb$^+$ cells become neurons while Numb$^-$ cells remain as neural stem cells.

Cell Differentiation. Figure 7 Asymmetric distribution of Numb. is distributed into one cell, which becomes negative for Hes1 expression. In contrast, the other cell, which does not receive Numb, expresses Hes1. Modified from [8].

the Numb$^-$ cells are maintained as neural stem cells. In the absence of *Hes1* and *Hes5* however, activator-type bHLH genes cannot be repressed and both daughter cells become neurons. Thus, cross-regulation between the activator-type and repressor-type bHLH genes through Notch signaling is essential to allow some cells to differentiate into neurons while keeping others as neural stem cells until later stages.

Regulation of Subtype Selection and Maturation

The subtype selection step is also regulated by bHLH genes. For example, excitatory neurons developed in the dorsal telencephalon are specified by *Neurogenin*, while inhibitory neurons developed in the ventral telencephalon are specified by *Mash1* [3,4]. Similarly, glial subtype selection, oligodendrocyte versus astrocyte, is regulated by the bHLH genes *Olig1/2*, *Hes1/5* and *Scl*. Thus, bHLH genes regulate not only the fate determination step but also the subtype selection step, indicating that these two steps proceed together. However, bHLH genes alone are not sufficient; other types of regulators such as homeodomain genes are required for subtype selection of many neurons. For example, in the dorsal spinal cord, the homeodomain gene *Lbx1* selects the GABAergic cell type, while the other homeodomain genes *Tlx1* and *Tlx3* select the glutamatergic cell type [9]. In the absence of *Lbx1*, the GABAergic neurons are transformed into glutamatergic neurons. Similarly, in the retina, combinations of bHLH and homeodomain genes are important for specification of neuronal subtypes. Different subtypes of retinal neurons are aligned in different layers, and this layer specificity is regulated by

homeodomain genes. Homeodomain genes alone cannot make neurons, but co-expression of bHLH and homeodomain genes can efficiently produce neurons with subtype specificity [10].

The maturation step of neurons is regulated by bHLH genes such as *NeuroD* and *Math2*, which belong to the family of activator-type bHLH genes. These bHLH genes seem to promote neurite extension and survival of immature neurons.

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Cell Membrane Components and Functions

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Synonyms

Plasma membrane – structure and functions; Plasmolemma – structure and functions

Definition

The ►nerve cell membrane is a microscopically thin membrane that separates the cell cytoplasm and intracellular organelles from the extracellular milieu. Its chemical composition and structural features allow free passage of most lipids, and selective passage of ions, sugars and amino acids. The membrane, in addition, contains the molecular machinery for cell-to-cell chemical and electrical communication and immune responsiveness.

Characteristics

Membrane Structure: Complex and Organized for Multi-tasking

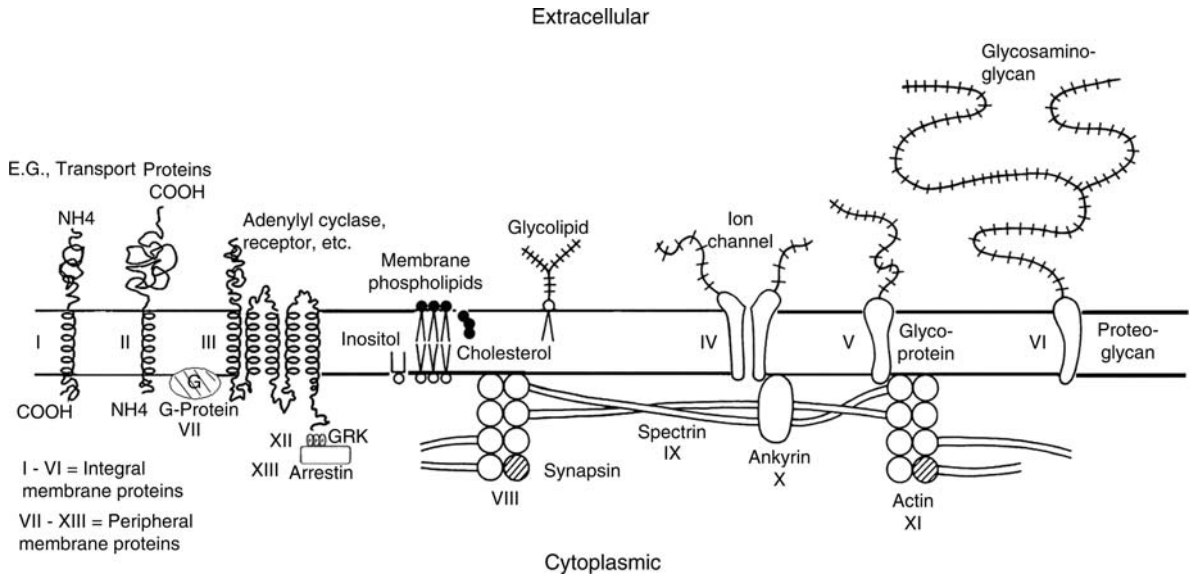
Until relatively recently the nerve cell membrane appeared to be a somewhat simple structure with a few simple, internal stereotyped tasks, whereas the accomplishment of complex neuronal tasks was thought to be the exclusive domain of networks of neurons. What we knew about membrane structure through the 1960's was comparatively modest. The membrane was unmistakably very thin, on the order of 50 nm. It was made up largely of proteins and lipids, the latter organized into a bilayer. It was electrically charged (polarized) at rest (►Membrane potential – basics). It had aqueous channels through which various ions passed that allowed the cells to be excitable, i.e., to generate ►action potentials for communication among cells. It was endowed with ►receptors, defined mainly by pharmacological testing, that enabled cells to communicate chemically through release and receptor binding of ►neurotransmitters. The membrane was also thought to somehow facilitate growth and development of ►neurites (dendrites and axons) for local and distant cell-cell communication.

The introduction of new methodologies beginning in the 1970's, including x-ray diffraction, freeze fracture electron microscopy, advances in crystallography, computerized methods for analysis and modeling, and an avalanche of molecular biological methodologies and discoveries, brought a new appreciation of cell membrane structural complexity; and with it, the discovery of heretofore unknown, built-in mechanisms of ►synaptic control and ►neuroplasticity.

This article provides a contemporary survey of membrane structural components, how they are assembled and how they contribute to nerve cell function.

Anatomy and Chemical Makeup of the Nerve Cell Membrane

The unit membrane of the nerve cell is depicted in Fig. 1. It is, on average, about 50 nm thick and comprised of various types of ►phospholipids, proteins and carbohydrates. Proteins, being the largest molecules, make up the greatest membrane mass but the smaller phospholipids are the largest in number and carbohydrate molecules are



Cell Membrane Components and Functions. Figure 1 Diagram of the nerve cell membrane. Shown are phospholipids, cholesterol, and various proteins (I–XIII) that make up membrane structure. See text for a description of their chemical properties and functions. Revised composite assembled from [4–6,10].

the fewest. The molecules making up the membrane proper, or attached to it, are mobile, interactive and in many cases functionally interdependent. They are replaced by intracellular biosynthesis, and turned over by a process called ►membrane trafficking.

Composition and Organization of Membrane Phospholipids

Membrane lipids are esters of glycerol phosphate attached to two long-chain fatty acids, each generally 14–20 carbon atoms long, and arranged in a bilayer with the glycerol phosphates facing the extracellular and intracellular fluids, and the fatty acid chains arranged in rows side by side in the membrane.

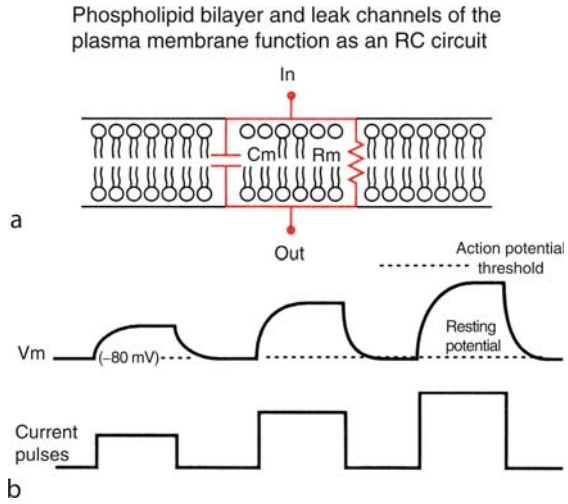
The phospholipid molecules are synthesized in the endoplasmic reticulum (ER), mainly in the cytoplasmic monolayer. Four different phospholipids are the major constituents of the bilayer: ►sphingomyelin, phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine. Smaller amounts of other phospholipids such as inositol phosphates are also found in the membrane. Phospholipids are differentially distributed in the cell membrane. More sphingomyelin and phosphatidylcholine are found in the outer leaflet of the bilayer, while more phosphatidylethanolamine and phosphatidylserine are found in the inner leaflet.

Phospholipid molecules have a high degree of lateral mobility in the bilayer, which facilitates movement of small nonpolar molecules across the cell membrane. Fluidity of cell membrane phospholipids also facilitates ►transport processes and enzyme activities. In fact, some membrane proteins require the presence of phospholipids for proper function. Less frequently, phospholipid molecules will "flip-flop," i.e., migrate from a monolayer on one side to that on the other.

Functions of Membrane Phospholipids

1. *Insulation and barrier properties*. The lipid bilayer acts as a barrier to passage of polar substances including water and electrolytes, although gases such as oxygen and carbon dioxide pass through it, along with various lipid–soluble substances including alcohol and local anesthetics. The barrier property protects the cell from loss of vital polar cytoplasmic constituents and entry of many potentially harmful extracellular substances.
2. *Intracellular signaling*. The phospholipid inositol 1,2,3-trisphosphate (IP3), formed by G-protein-mediated activation of phospholipase C on the cytoplasmic side of the cell membrane, is a ►second messenger that mobilizes release of Ca^{2+} and thus activation of Ca^{2+}-dependent intracellular processes.
3. *Electrical properties*. The phospholipid bilayer, along with open ion ►(leak) channels of the cell membrane, acts as a ►resistance-capacitance (RC) circuit (Fig. 2a) as well as a low-pass filter and integrator of electrical input signals.

The extremely thin, expansive lipid bilayer of the nerve cell membrane has a ►membrane capacitance on the order of 1 $\mu F/cm^2$ that produces a charge of about 8×10^{-9} coulombs/cm^2 at a ►resting membrane potential (membrane potential – basics) of –80 mV, or approximately 5×10^{11} monovalent ions/cm^2. Even



Cell Membrane Components and Functions.
Figure 2 Membrane capacitance and resistance, and effect on membrane current. (a) The membrane phospholipid bilayer acts as a capacitor, and membrane proteins assembled as ion channels provide a pathway with resistance for current flow. (b) The transmembrane voltage response (Vm) to current pulses of different intensity. Revised from [7].

under steady state, or resting conditions, membrane channels, including some K^+ and Na^+ channels, stay open and generate a "►leak conductance" [1]. In effect, what results is a leaky RC circuit, with a specific membrane resistance of about 1,000 Ωcm^2 [2].

The RC circuit properties have functional consequences (Fig. 2b). In the resting state, the net movement of K^+ ions down its concentration gradient through leak channels will leave behind impermeant cytoplasmic organic anions that accumulate on the inner side of the cell membrane and an accumulation of cations on the extracellular side [3], which accounts for the potential difference (Vm) of about −80 mV across the cell membrane (membrane potential – basics).

Figure 2b also shows subthreshold membrane potential responses to square wave pulses of current applied through a microelectrode inserted through the cell membrane (also membrane potential – basics). Each depolarizing current pulse will first mainly charge the membrane capacitor, and then the voltage difference will promote ion movement through the leak channels. The consequence is that the voltage transients caused by the applied current steps from the microelectrode develop more gradually than the current changes. Synaptically evoked ►postsynaptic potentials (PSPs) will also build up more slowly than their corresponding synaptic currents. The RC properties of the membrane act as a low-pass filter, and an integrator of PSPs if frequency of occurrence leads to temporal summation. They can also affect the time required for an action potential to reach threshold, and consequently the interspike interval during a burst of action potentials.

Cholesterol

The nerve cell membrane contains large amounts of ►cholesterol, which is synthesized mainly in the endoplasmic reticulum (ER). Cholesterol enhances the permeability-barrier property of the lipid bilayer. The hydroxyl groups of cholesterol are in proximity to the polar heads of the phospholipid molecules (Fig. 1) and partially immobilize the hydrocarbons close to the polar heads. This renders the lipid bilayer less permeable to small water-soluble molecules.

Glycolipids

These lipids contain carbohydrate groups, usually galactose but also glucose, inositol or others, and are found only on the extracellular side of the cell membrane. ►Glycolipids associate into micro-aggregates and are believed to be involved in cell-cell interactions. Five to ten percent of the total lipid mass consists of a particular type of glycolipid called a ►ganglioside.

Gangliosides are thought to alter the electrical field across the cell membrane, as well as the concentration of Ca^{2+} ions along the external surface of the cell membrane. They may also be involved in cell-cell recognition at the extracellular matrix that promotes cell aggregation.

Membrane Proteins

Figure 1 illustrates only 13 of a much larger group of currently identified and characterized membrane proteins. Proteins are subdivided according to position into integral (types I-V in Fig. 1) and peripheral (VI–XIII). ►Integral proteins completely traverse the cell membrane, whereas ►peripheral proteins are anchored to either the cytoplasmic or extracellular side. Singer [4] subdivided integral proteins into four general types, I–IV. Types I and II have just one transmembrane segment, and terminal amino and carboxyl groups on opposite sides of the cell membrane. Some transport proteins are part of this group. Members of the Type III group, which include the β−►adrenergic receptor and adenylyl cyclase, an intracellular signaling component, have polypeptide chains that traverse the cell membrane several times. Members of type IV, which includes ►ion channels, have several domains that are arranged around an aqueous pore that serves as the channel. Hydrophobic parts of integral proteins are positioned within the cell wall, in parallel with the lipid bilayer. Hydrophilic parts of integral proteins face the cytoplasm and extracellular fluid. The proteins have some degree of lateral mobility, less so than phospholipids.

Membrane proteins exhibit function-dependent polarity. For example, transporting enzymes have ATP-binding sites on the cytoplasmic side and glycoproteins have sugar residues on the outer surfaces.

Synthesis of cell membrane proteins takes place largely in the soma endoplasmic reticulum (ER), under the direction of nuclear DNA in ribosomal RNA-protein complexes. Selective axonal and dendritic transport processes deliver proteins to all regions of the neuron. Rough ER bears the ribosomes during protein synthesis. Newly synthesized protein is stored in cisternae, transported in vesicles through the Golgi apparatus and inserted into the cell membrane.

Cell membrane proteins are also synthesized on polyribosomes and stored in membranous cisterns in dendrites and axons, where they play important roles in ►synaptic plasticity and ►axon growth.

Functions of Membrane Proteins

The locations of different types of proteins in the cell membrane serve as general predictors of how they function in the nerve cell.

Integral membrane proteins serve as:

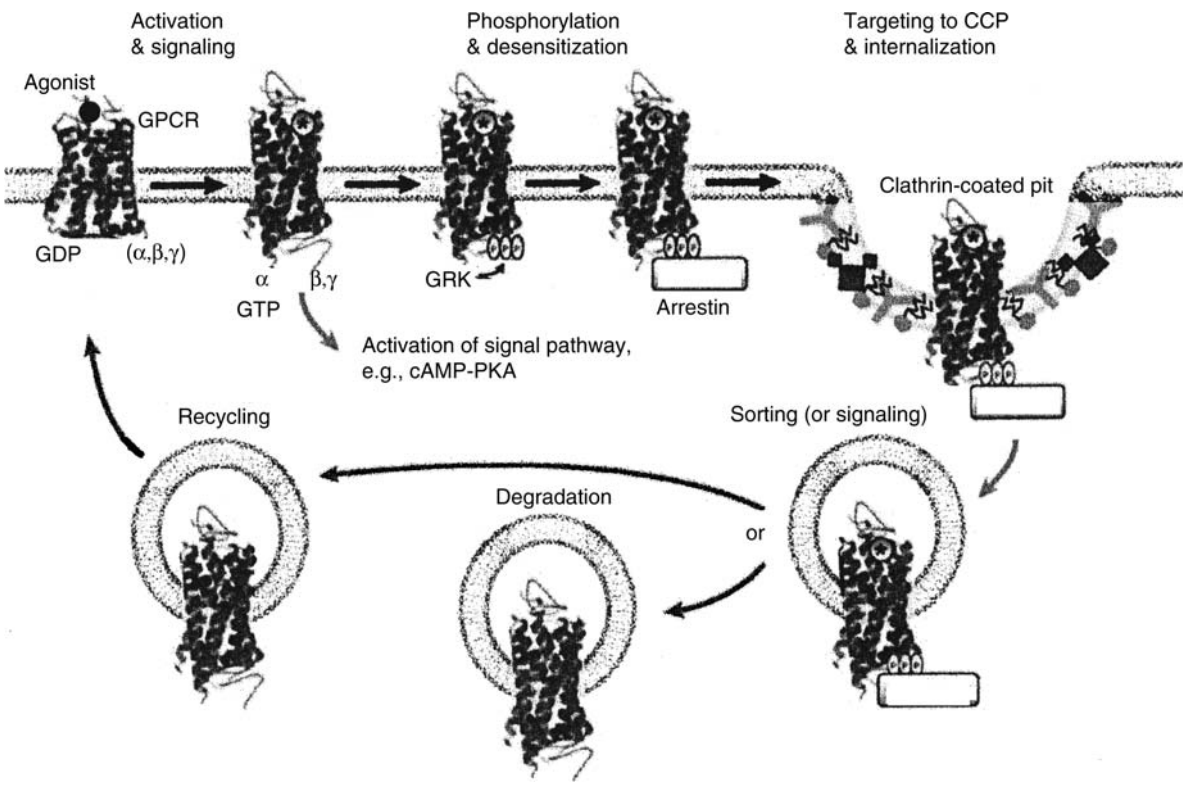
1. ►Ion pumps, moving ions against a concentration gradient, using energy derived form ATP
2. Ion channels, allowing flow of ions and water across the cell membrane down an electrochemical gradient
3. Transporters of sugars and amino acids
4. Cell-cell recognition sites

Glycoproteins have three main subgroups, each involved one way or another with cell-cell recognition: the immunoglobulin super-family, the cadherin family and the integrins. The immunoglobulin family imparts Immunoreactivity, homophilic cell-cell interactions and outgrowth of neurites and fiber bundling during development. The cadherin family promotes Ca^{2+}-dependent neurite growth and axon bundling. The integrins promote cellular interactions with the extracellular matrix and also promote neurite growth and extension of axons to their targets.

►Proteoglycans, another group of integral proteins thought to be involved in cell-cell recognition, have long sugar chains that form a structure around the cell called the ►glycocalix that is important for structural support.

Peripheral proteins function as:

1. Receptors for neurotransmitters, ►neuromodulators, ►hormones and other chemical messengers that trigger membrane ion permeability changes.



Cell Membrane Components and Functions. Figure 3 Trafficking (cycling) of a G protein-coupled receptor (GPCR) under the influence of GPCR kinase (GRK) and Arrestin. After agonist binding and G-protein-mediated activation (or suppression) of a signal pathway, GRKs phosphorylate GPCR and Arrestin forms a complex that terminates signaling and translocates the complex to a clathrin-coated pit, followed by internalization and either degradation or recycling. Adapted from [6].

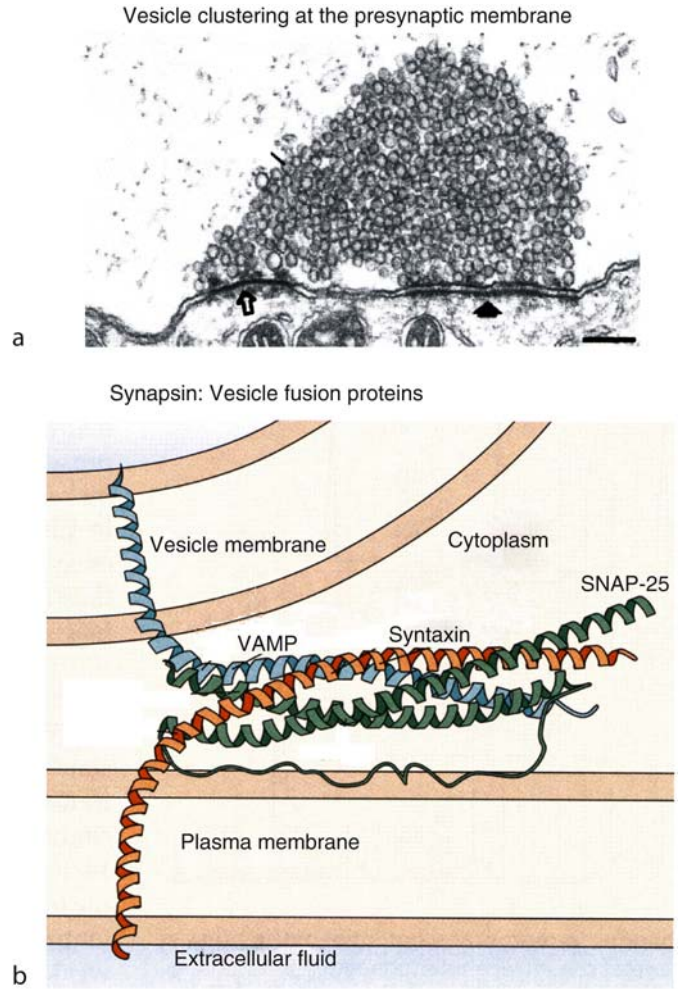
2. Enzymes that catalyze intracellular signal cascades.
3. Immunoreactive elements.
4. Membrane structural support proteins, such as ►actin, ankyrin, fodrin, and spectrin.
5. Mediators of neurite outgrowth and axon bundling
6. Intermediaries in membrane trafficking, a term that applies to recycling of agonist-activated receptors and ►synaptic vesicles. These processes are central to the development of desensitization to neurotransmitters and drugs and cell-cell communication.

Receptor Recycling and the Development of Desensitization

The fidelity of chemically mediated ►synaptic transmission is affected by the affinity of an agonist for a receptor and by the number of available receptors. Each of the two factors plays a key role in neural network responsiveness to endogenous ►neurohumoral agents as well as drugs such as ►opiates.

Desensitization of response to a ►receptor agonist most often occurs after prolonged or repeated receptor binding, particularly if the agonist has a high affinity for the receptor.

As shown in Fig. 3, binding of the agonist to its receptor triggers activation of several cytoplasmic membrane proteins, including G-Protein-coupled receptor kinases and a family of proteins known as ►arrestins. The consequence is internalization of the receptor, which is either degraded or reincorporated into the cell membrane.



Cell Membrane Components and Functions. Figure 4 Vesicle exocytosis and synaptic membrane proteins. (a) Electron micrograph of a lamprey reticulospinal, axodendritic synapse. A cluster of synaptic vesicles containing neurotransmitter is seen next to the presynaptic membrane. Active zones on the membrane where exocytosis occurs are distinguished by the dark bands and filled arrow (*open arrow* points to a gap junction). (b) Synapsins (proteins that bind vesicles to the presynaptic membrane) are shown, such as VAMP (synaptobrevin), SNAP-25 and Syntaxin. Adapted from (a): [8]; (b): [9].

Vesicle Recycling and Neurotransmitter Release

Release of neurotransmitter into the ►synaptic cleft is contingent on binding and incorporation of vesicles containing the secretory substance to the presynaptic membrane, at specialized release sites called ►active zones. Figure 4 illustrates an electron micrograph of a synaptic cleft, with vesicles positioned for release at the active sites (Fig. 4a), and a cartoon of the different proteins that affect binding of the vesicle to a release site (Fig. 4b).

Summary

The nerve cell membrane consists of a functionally efficient organization of phospholipids, proteins and carbohydrates that orchestrate static functions such as insulation and membrane electrical charge, and dynamic functions related to cell excitability, cell-cell communication and cell responsiveness to receptor agonists.

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Cell Signaling

►New Developments in G Protein-Coupled Receptor Theory

Cell Soma

Definition

The cell soma is the body of a neuron as apposed to its dentritic and axonic processes.

Cell Transplantation

►Autoimmune Demyelinating Disorders: Stem Cell Therapy

Cellular and Humoral Immunity

Definition

Cellular immunity utilizes phagocytes (such as macrophages, neutrophils, and eosinophils), which engulf antigens, and T-lymphocytes, which are thymus-derived, antigen-specific immune cells containing receptors specific for a special antigen. Cellular immunity is particularly important in defending the body against tumors and infections. Macrophages phagocytize antigens and secrete proteins (cytokines) that regulate cells involved in immune responses. One cytokine is interleukin-2, which stimulates an increase in the number of T-lymphocytes. The T-lymphocytes then develop surface receptors for specific antigens.

Because T-lymphocytes survive for months or years, cellular immunity toward the antigen remains with the individual for a long time. If re-exposed to the same antigen, the sensitized T-lymphocytes recognize the antigen and secrete their own proteins (lymphokines), which stimulate phagocytes to destroy the antigen. If an antigen is located on foreign or tumor cells, certain Tlymphocytes are transformed into cytotoxic T-lymphocytes, which destroy the target cells.

Humoral immunity utilizes antibodies, also known as immunoglobulins (Ig), produced by B-lymphocytes. Blymphocytes are lymphocytes derived from the spleen, tonsils, and other lymphoid tissues. They become plasma cells, which make antibodies. There are five classes of antibodies: IgG, IgM, IgA, IgD, and IgE. IgG, IgM, and IgA are involved in humoral immunity, the function of IgD is not known, and IgE takes part in immediate hypersensitivity. Humoral

immunity involves the inactivation, removal, or destruction of antigens. Antibodies can inactivate viruses by binding to them.With two antigen binding sites per protein unit, an antibody can also precipitate the antigen by crosslinking in a network formed with other antibodies. After the antigen is precipitated, it can be removed by phagocytes. In addition, antigen binding by IgG or IgM activates a serum protein, called a complement, which can then initiate antigen precipitation, amplifying the inflammatory response. If the antigen is on the surface of certain cells, activated complement can also facilitate the lysis of these cells. IgG or IgM can also link the antigen to phagocytes or to killer cells, resulting in lysis of the cell by an unknown mechanism.

Cellular Clock

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Synonyms

Cellular oscillator

Definition

Cellular clock refers to the intrinsic physiological mechanisms by which cells function as autonomous circadian oscillators. There are similarities and differences between the cellular clock mechanisms of plants, fungi, animals, and prokaryotes.

Characteristics

Cellular Clocks Can Function Autonomously

One of the key features of many cellular clocks is that they can function autonomously, i.e., they do not require intercellular communication. A seminal experiment demonstrating this revealed that mammalian ►circadian pacemaker neurons cultured under conditions where synaptic communication is abolished continue to exhibit circadian rhythms of action potential firing rate [1]. This leads to the conclusion that circadian oscillation is an intrinsic property of the cell itself, and is not solely a tissue-level phenomenon. This constrains the search for underlying mechanisms of circadian oscillation to processes that occur at the cellular level. Nevertheless, intercellular communication at the tissue level and communication between different tissues at the organismic level play important roles in the integrative physiology of circadian timekeeping.

Cellular Clocks Involve Negative Transcriptional Feedback

A key common feature of the cellular clock in fungi, plants, and animals is negative transcriptional feedback, a mechanism in which a gene product negatively regulates the gene that encodes it [for review, see 2]. Many "clock proteins" are transcription factors that, upon nuclear entry from the cytoplasm where they are synthesized, inhibit transcription of the "►clock genes" that encode them. This mechanism ensures that when clock protein levels increase, there is a decrease in clock gene transcription, and consequent decrease in clock protein synthesis. In conjunction with clock protein degradation, this leads to a decrease in clock protein levels. This results in release from inhibition of clock gene transcription, and a consequent increase in clock protein levels, thus completing one cycle of an oscillation in the abundance of both clock gene transcripts and, with a delay, clock proteins.

Cellular Clocks Involve Post-Translational Covalent Modification of Clock Proteins

While this simple model of the cellular clock explains how negative transcriptional feedback can underlie a ►self-sustaining oscillation of clock gene transcript and clock protein abundance, it does not account for the fact that circadian ►oscillators cycle with a ►period very close to 24 h. The period of oscillation is determined by the time occupied by each of the steps of the cycle outlined above: transcription of clock gene, translation of clock gene transcript into clock protein, nuclear import of clock protein, degradation of clock protein. The most important mechanisms for setting the period of oscillation of the cellular clock appear to be regulation of the rates of nuclear import and degradation of clock proteins, implemented via post-translational modification of clock proteins [for review, see 3]. The two main post-translational modifications of clock proteins are protein phosphorylation – the covalent attachment of phosphate groups – and ubiquitination – the covalent attachment of the small polypeptide ubiquitin. Phosphorylation of clock proteins catalyzed by protein kinase enzymes regulates both nuclear import and ubiquitination. Ubiquitination of clock proteins catalyzed by ubiquitin ligase enzymes regulates degradation. Clock proteins can also be dephosphorylated and/or deubiquitinated by protein phosphatases and ubiqutin-specific proteases, respectively. Thus, the balances of phosphorylation and dephosphorylation, and of ubiquitination and deubiquitination, ultimately determine the period of oscillation of the cellular clock, with an appropriate balance resulting in a period of oscillation close to 24 h. Point mutations either in clock-protein transcription factors or the kinases that phosphorylate them that affect phosphorylation lead to aberrant periods substantially shorter or longer than 24 h. Some of these

point mutations have been implicated in human disorders of circadian regulation of the ►sleep-wake cycle [for review, see 4].

Cellular Clocks do not Always Require Negative Transcriptional Feedback

While most cellular clocks appear to require negative transcriptional feedback, circadian oscillation in cyanobacteria – photosynthetic prokaryotes – can occur under some circumstances in the complete absence of transcription altogether. When a completely purified cyanobacterial clock protein that has protein kinase activity is incubated in a test tube with ATP, the clock protein itself exhibits a circadian rhythm in its level of phosphorylation [5]. Since this rhythm occurs in a reconstituted cell-free system without any gene transcription or protein translation, it establishes the existence of cellular clock mechanisms that do not rely on negative transcriptional feedback.

Cellular Clocks Can Require Membrane Depolarization

In addition to negative transcriptional feedback and post-translational modifications, some circadian pacemaker neurons require membrane depolarization for continued oscillation (for review, see [6]). When the plasma membrane of fruit fly or mammalian pacemaker neurons is chronically hyperpolarized, cellular oscillation is severely impaired. Interference with intracellular calcium signaling also severely impairs cellular oscillation. These kinds of studies have led to a model of cellular oscillation in which circadian rhythms of membrane potential and/or intracellular calcium also participate – along with negative transcriptional feedback – in circadian timekeeping.

Cellular Clocks are Temperature Compensated

One of the most fascinating features of cellular clocks is that they are ►temperature compensated, meaning that they run with the same period at a relatively wide range of temperatures. Since cellular clocks are based on a complicated set of interlocking biochemical reactions, and since the rates of biochemical reactions have a temperature dependence determined by principles of thermodynamics, then the simplest prediction would be that the period of cellular oscillation would also be temperature dependent. The fact that cellular clocks are temperature compensated thus implies the existence of specific compensatory mechanisms that counteract the effect of temperature on the biochemical reactions that underlie cellular timekeeping. While the nature of these compensatory mechanisms remains obscure, it is noteworthy that the reconstituted cell-free cyanobacterial oscillator is temperature compensated [5].

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Cellular Oscillator

►Cellular Clock

Cellular Potency

Definition

Potential of a given (primary) cell to differentiate into a number of daughter cell fates. In cell biology, cellular potency varies from pluri- to uni-potency. Pluripotency has come to refer to a stem cell that has the potential to differentiate into any of the three germ layers: endoderm (e.g., interior stomach lining, gastrointestinal tract, the lungs), mesoderm (e.g., muscle, bone, blood, urogenital), or ectoderm (e.g., epidermal tissues and nervous system). Pluripotent stem cells can eventually specialize in any bodily tissue, but they cannot themselves develop into a human being because they cannot develop into extraembrionic tissue, such as the placenta. In contrast, many progenitor cells (e.g., adult stem/progenitor cells) are multipotent (e.g., capable of generating a limited number of cell fates).

Totipotent stem cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent. These cells can differentiate into embryonic and extraembryonic cell types.

Pluripotent stem cells are the descendants of totipotent cells and can differentiate into cells derived

from the three germ layers. Multipotent stem cells can produce only cells of a closely related family of cells (e.g., neural stem cells differentiate into neurons, oligodendrocytes, astrocytes).

Unipotent cells can produce only one cell type, but have the property of self-renewal which distinguishes them from non-stem cells.

Center of Mass (CoM)

Definition

The center of mass is the point in or near the body where total body mass is concentrated and about which the body would balance without a tendency to rotate. Center of mass of the body is a function only of the locations and masses of individual body segments. As a result, it varies with body build, posture, gender, and age. For an average individual standing erect with arms at the side the center of mass location is just anterior to the lower lumbar/upper sacral vertebrae. Also known as the center of gravity, because the vertical gravitational force due to the weight of the body can be considered to act through this point. Based on Newton's second law of motion, the net actions of external forces and torques acting on the body, computed with respect to the center of mass, determine the net acceleration of the body.

►Postural Strategies
►Postural Synergies

Center of Pressure

Definition

The centroid of the pressure distribution exerted by the body on the ground. It is the point in the support surface where the resultant of the vertical force components acts, causing a force, but no moments.

►Motion Analysis
►Stabilometry

Center-surround Antagonism

Definition

Retinal ganglion cells and lateral geniculate nucleus relay cells have receptive fields made of two concentrically arranged subregions, a disk shaped "center" and an annular "surround." The boundaries between subregions are defined by different preferences for stimulus contrast (bright or dark) or sometimes by preferences for stimulus wavelength (color).Within On subregions, bright stimuli excite and dark inhibit, with the reverse profile for Off subregions. Because of this push-pull relationship between stimuli of opposite contrast, neighboring subregions have an antagonist effect on each other when both are filled with a spatially uniform stimulus.

►Lateral Geniculate Nucleus
►Retinal Ganglion Cells
►Visual Cortical and Subcortical Receptive Fields

Center-surround Receptive Fields

►Visual Cortical and Subcortical Receptive Fields

Central Amygdaloid Nucleus

Synonyms

Nucl. amygdalae centralis; Central amygdaloid nucleus

►Amygdaloid Body
►Telencephalon

Central Cerebellar Nuclei

Synonyms

Nuclei cerebelli; Cerebellelar nuclei

Definition

The central cerebellar nuclei are located partly in the vermis cerebelli (fastigial nucleus, emboliform nucleus, globose nucleus) and partly in the medulla of the hemispheres (dentate nucleus). Their afferents have their origin in the Purkinje cells of the cerebellar cortex. The cells of the cerebellar hemisphere, lateral part project to the dentate nucleus, the cerebellar hemisphere, intermediate part to the emboliform nucleus and globose nucleus and the vermis cerebelli to the fastigial nucleus.

►Cerebellum

Central Chemoreception

Definition

Central chemosensitive neurons, which are sensitive to pH alteration in the cerebrospinal fluid, are tonically active and continuously activate the respiratory neurons. This tonic excitation may be synaptically transmitted to each respiratory neuron during the active phase and be gated during the inactive phase by periodic waves of inhibitory postsynaptic potentials (IPSPs).

►Central Nervous Chemoreceptors and Respiratory Drive
►Cerebrospinal Fluid (CSF)

Central Chemoreceptor

Definition

A chemoreceptor which exists within the central nervous system.

►Central Nervous Chemoreceptors and Respiratory Drive
►Respiratory Reflexes

Central Cholinesterase Inhibitors

Definition

Drugs that inhibit the enzyme acetylcholine esterase in the central nervous system, thus increasing the levels of acetylcholine in the brain.

Central Core Disease (CCD)

Definition

A rare, nonprogressive myopathy often present at infancy, which is characterized by hypotonia and proximal muscle weakness. In most cases. CCD has been linked to mutations in the *RyRI* gene encoding the Ca^{2+} release channel of the sarcoplasmic reticulum. Diagnosis is made on the basis of the lack of mitochondria and oxidative enzyme activity in central regions of skeletal muscle cells, observed upon histological examination of muscle biopsies.

►Excitation-Contraction Coupling

Central Gray Matter

Synonyms

Substantia grisea centralis; Periaqueductal gray substance

Definition

The central gray matter, also called periaqueductal gray matter, surrounds the mesencephalic aqueduct in the Mesencephalon, passing far into the metencephalon. Hence a distinction is made between:

- Central gray matter of Mesencephalon
- Central gray matter of metencephalon

The centrally located band of cells is an autonomic integration center, akin to the reticular formation. It receives afferents from virtually all parts of the brain and regulates e.g. coordination of the cranial nerve nuclei (e.g. swallowing). By virtue of the close interaction with the limbic system, the central gray matter is also involved in affective fear and flight reactions as well as in pain suppression.

►General CNS

Central Integration of Cardiovascular and Respiratory Activity Studied In Situ

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Synonyms

Arterially perfused brainstem; Autonomic nervous system; Sympathetic; Parasympathetic; Automatic ventilation; Coupling between cardiovascular and respiratory control systems; Respiratory sinus arrhythmia

Definition

Within the brainstem there are neural circuits that control visceral functions; these are independent of

conscious control. One such network regulates the cardiovascular system by controlling ►autonomic (►nervous system) motor outflow (i.e., sympathetic and parasympathetic) to target organs such as the heart, arterioles and adrenal glands, for example. The activity within this network is, in part, generated from within the central nervous system itself. Part of this originates from the brainstem respiratory rhythm generator which is coupled synaptically to neurons controlling autonomic cardiovascular activity. Another source of excitation comes from sensory peripheral afferents that provide feedback signals. Both the latter as well as centrally generated inputs are computed (i.e., integrated) by neurons regulating arterial pressure and/or respiration. In this sense, the control of the cardiovascular and respiratory systems are coupled together allowing a matching of cardiac output with minute ventilation, which is crucial for optimizing physiological function. This system can be studied ►in situ, which is neither in vitro nor in vivo. In situ is the study of either an organ or organs (and their interactions) maintained viable within their own body space. Here, an in situ preparation containing much of the cardiovascular system and brainstem will be reviewed in terms of recent advances regarding our understanding of central neural integration of cardiovascular and respiratory function.

Characteristics

The In Vitro Approach

An enormous amount of information has been gained from in vitro mammalian brain preparations. Examples range from the discovery of long term potentiation to mechanisms of synaptic transmission and oscillatory neuronal behavior, as well as imaging of somatic and dendritic integration. The in vitro brain slice preparations evolved from the need to circumnavigate the technical obstacles and limitations encountered when working on the brain in vivo. Indeed, in vitro brain slice preparations are advantaged by the ability to control precisely multiple physiological variables (e.g., temperature; osmolarity) as well as the extracellular milieu thereby enabling the administration of pharmacological agents that include those that would be toxic if administered in vivo. Of major benefit is the mechanically stable environment of in vitro brain slice preparations. For example, maintaining intracellular recordings in vivo is plagued by the constant movement of the brain caused by the cardiac pulse and/or breathing cycle. With the significant advances in live imaging at the cellular level, brain slices, particularly those from neonates (which are more transparent as myelination is incomplete), allow visualization of cells (neurons, glia or vessels) and measurement of intracellular events such as calcium fluxes and translocation of fluorescently tagged proteins. Importantly, the brain slice is ►insentient and data are not compounded by the unphysiological effects of anesthesia.

The Drive to Go In Situ

The viability of the brain slice is determined by its thickness. Thus, the neuronal circuitry and connectivity is restricted. Without a circulation oxygen delivery is dependent on diffusion. This is limited as demand for oxygen by brain tissue is relatively high. To assist in delivery, high concentrations of oxygen are used (95% with 5% carbon dioxide, or carbogen) to elevate the diffusion gradient. Measurements in slices indicate that the tissue oxygen levels at the surface of the slice are hyperoxic (►hyperoxia) but levels decline rapidly such that anoxia occurs by 150–175 μm below the surface [1]. En-bloc brainstem and brainstem-spinal cord preparations of neonatal rats have been used in cardiovascular and respiratory research but these are known to have an anoxic core and viability is limited to the early neonatal period only. To improve the viability of thicker in vitro brain preparations and to allow studies to be performed on adult tissues, researchers developed arterially perfused in vitro preparations which, for example, included those of the brainstem [2] and cerebellum.

The In Situ Approach

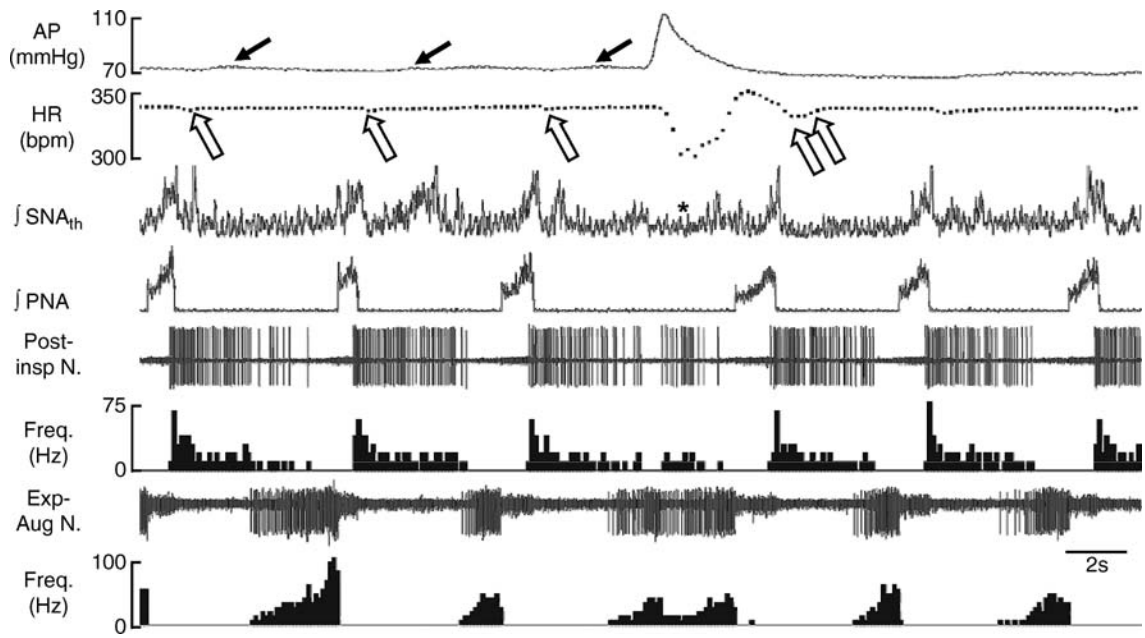
Despite these technological advances, there was a requirement to study the brain in situ. In situ means studying the brain within the body of the animal. This had the distinct advantage over isolated in vitro brain preparations (slice, en bloc, arterially perfused) of not only preserving both significant regions of the brain but also maintaining the peripheral afferent pathways and their peripheral receptors intact. It was apparent that the motor pathways were also preserved allowing ►kinesiological (►Kinesiology) studies as target organs were functional. Motor outflows (autonomic and somatic) could be shown to respond appropriately to stimulation of classical reflex pathways such as those mediating nociception, baroreceptor and peripheral chemoreceptor information. With such integrity of the in situ preparation, the question of how it was different to in vivo preparations and what added benefits there were arose. The in situ approach is distinct to in vivo in that anesthesia could be avoided by decortication or decerebration, the pulse pressure that caused mechanical instability in vivo was either minimized or abolished meaning the brainstem was more receptive to intracellular recording and imaging (see below). If forebrain structures were required then anesthetic agent could always be added to the perfusate. Finally, there was good pharmacological access as drugs could be applied topically or to the perfusate. A number of in situ preparations from multiple researchers using a variety of species have been utilized previously (e.g., [3]) and

all demonstrated superior mechanical stability of the brainstem relative to in vivo rats and the ability to antagonize receptors with drugs given systemically.

The In Situ Working Heart-Brainstem Preparation

Since 1995 three new in situ preparations have been developed (i) the working heart-brainstem preparation (WHBP; [4]); (ii) the perfused hind limb and trunk preparation and, (iii) the decerebrate arterially perfused whole rat preparation [5]. In all cases, the preparations were perfused arterially with a cell-free perfusate consisting of a Ringer's solution containing an oncotic agent (to prevent edema) with an osmolarity of 290 mosm.kg^{-1}.H_2O and gassed with carbogen (pH 7.35) at 31–33°C. All these variables can be "clamped" or manipulated as the experiment demands. No oxygen carriers were required. This was a major benefit as they are both expensive and difficult to dissolve in aqueous solution. Adequate oxygenation is achieved because the perfusate is less viscous than blood allowing higher flow rates to be used for a given arterial pressure. Additions of vasopressin to the perfusate were effective in increasing vascular tone allowing long term manipulation of perfusion pressure to within physiological or hypertensive levels (Fig.1).

The lower temperature than normal 31–33°C reduces metabolic rate so reducing oxygen usage. As a result, the oxygen supply satisfies demand. Indeed, measurements of PO_2 throughout the brainstem of the WHBP demonstrated that even at its core there is plenty of oxygen; in fact, the preparation is some what hyperoxic [6] such that 70–75% oxygen would maintain PO_2 at a physiological level. Thus, both the lower temperature and hyperoxic nature are potential drawbacks of this approach. At all depths within the brainstem pH was constant and reflected that of the perfusate (e.g., 7.35; [6]). An additional benefit of these preparations is the speed at which they can be set-up. The in situ preparation typically takes 20 min. A comparable in vivo animal may take several hours to establish. Moreover, the preparations can be made from most small mammals of up to 150 g of either adult or neonatal age and have included: mouse, rat, shrew and guinea pig. Because neonatal rats can be used (from day zero) developmental studies can be made in the



Central Integration of Cardiovascular and Respiratory Activity Studied In Situ. Figure 1 Integrating across systems in situ. Simultaneous recording of arterial pressure (AP), heart rate (HR; beats per minute, bpm), integrated thoracic sympathetic activity (SNA$_{th}$), integrated phrenic nerve activity (∫PNA) and two expiratory neurons from the Bötzinger complex. Note the Hering-Traub waves in the arterial pressure trace (solid arrow) and the sinus arrhythmia (*open arrow*); the former reflect the respiratory-related increase in sympathetic discharge whereas the latter indicate heightened excitability of cardiac vagal motoneurons in early expiration. Stimulation of the baroreceptor reflex by raising systemic pressure (achieved by increasing perfusion pump rate transiently) reduces both heart rate and SNA(*) but prolongs expiratory time which is coincident with an activation of the post-inspiratory neuron (Post-Insp) and an inhibition of the expiratory augmenting (Exp-Aug) neuron. Note the prolonged post-inspiratory neuron firing and enhanced sinus arrhythmia (*two open arrows*) after the baroreceptor stimulus. Unpublished (D. Baekey, T. E. Dick & J. F. R. Paton).

same preparation, which is advantageous and essential for direct comparisons with age. The preparation is free from anesthesia as the brain is decerebrated precollicularly, which removes the compounding problems relating to anesthesia but also means that forebrain structures are absent.

The WHBP consists of the thorax, neck and head with lower body (below the diaphragm) removed. It is perfused retrogradely via the descending aorta and within minutes respiratory movements of the chest and diaphragm resume and phrenic nerve discharges with an augmenting pattern characteristic of ►eupnea (Fig. 1). The eupneic-like respiratory pattern generated spontaneously for many hours by the in situ preparation is analogous to that generated by in an in vivo unanesthetized decerebrate rat. It was this "normal" pattern of inspiratory neural discharge that was essential for establishing the viability of the preparation. However, the respiratory frequency of the WHBP is considerably slower than that reported in vivo and in this regard the breathing is not eupneic. However, the slow respiratory rate was found to be a product of the lower running temperature (31–33°C) and absence of pulmonary vagal afferent feedback resulting from lung inflation [7]. Lung inflation is not required as the perfusate is aerated with carbogen but if the lungs are inflated mechanically and if perfusate temperature is raised to 37°C then breathing rates are close to those observed in decerebrate rats in vivo.

The Integrative Aspect of the Working Heart-Brainstem Preparation

The integrative nature of the WHBP is portrayed by the central nervous coupling between multiple systems. Fig. 1 shows that the preparation exhibits respiratory sinus arrhythmia that occurs naturally to assist the matching of cardiac output with minute ventilation. This has a central nervous correlate with the firing of neurons located in the ventrolateral medulla. These are expiratory neurons exhibiting a decrementing discharge that fire maximally coincident with the onset of the sinus arrhythmia bradycardia (Fig. 1). The firing of these neurons occurs at an identical time as well as exhibiting a similar pattern to the decrementing expiratory motor activity recorded from the central vagus nerve. This decrementing (post-inspiratory) motor activity targets cardiac vagal post-ganglionic neurons but also laryngeal adductor muscle. Interestingly, it is possible to measure the respiratory phase-dependent changes in laryngeal resistance in the preparation, which is a good example of how the preparation offers a ►kinesiological approach. Respiratory modulation of the airway acts to facilitate inhalation (upper airway ►abduction) as well as stalling exhalation (laryngeal ►adduction) to prolong time for gas exchange at the level of the alveoli. In addition, sympathetic nerve activity is also respiratory phase modulated peaking at the transition between the end of inspiration and start of expiration (Fig. 1). Again, expiratory neurons (Bötzinger augmenting type) show a similar firing pattern and temporal relationship with sympathetic nerve activity (Fig. 1).

The WHBP has contributed to the understanding of central integration of cardiovascular and respiratory reflexes. These include reflexes originating from nociceptors (somatic and visceral), peripheral chemoreceptors, cardiac, pulmonary, nasal, pharyngeal and oesophageal receptors. Additionally, the baroreceptor reflex is functional evoking the classical response of bradycardia, sympathoinhibition and prolongation of expiratory time (Fig. 1). Incidentally, the gain of the cardiac baroreceptor reflex is comparable to that measured in the conscious unrestrained rat (i.e., ∼1.8 bts/min/mmHg). With the ability to precisely control arterial pressure, including its resting level, we were able to demonstrate a difference in the pressure threshold for baroreceptor reflex evoked vagal bradycardia versus sympathoinhibition. This lead to the new idea of separate reflex sympathetic and parasympathetic arcs existing at the level of the nucleus tractus solitarii, the site of termination of baroreceptor afferents [8]. In addition, for the first time baroresponsive cells were recorded intracellularly from the nucleus tractus solitarii using ►whole cell patch recording, while stimulating the baroreceptors using the physiological stimulus of pressure. This has allowed novel insight into their subthreshold activity, intrinsic membrane properties and morphology, for example. The WHBP has also played an important role in the introduction of viral gene transfer as a method to unravel central mechanisms involved in regulating the sensitivity of the baroreceptor reflex at the level of the nucleus tractus solitarii [9]. In the absence of a pharmacological antagonist for endothelial nitric oxide synthase (eNOS), adenoviral gene delivery of an eNOS dominant negative was used to demonstrate that the well established depressant effect of angiotensin II acting at the level of the nucleus tractus solitarii on baroreceptor reflex gain was via production of nitric oxide generated by stimulation of eNOS. This led to the novel idea of *vascular-neuronal signaling* in which paracrine signaling by chemical messengers released from the endothelium, such as nitric oxide, cross the blood brain barrier to affect neural processing of baroreceptor reflex circuitry. Subsequently, it was functionally shown that this process plays an essential role in the homeostatic reflex regulation of arterial pressure in both health and disease.

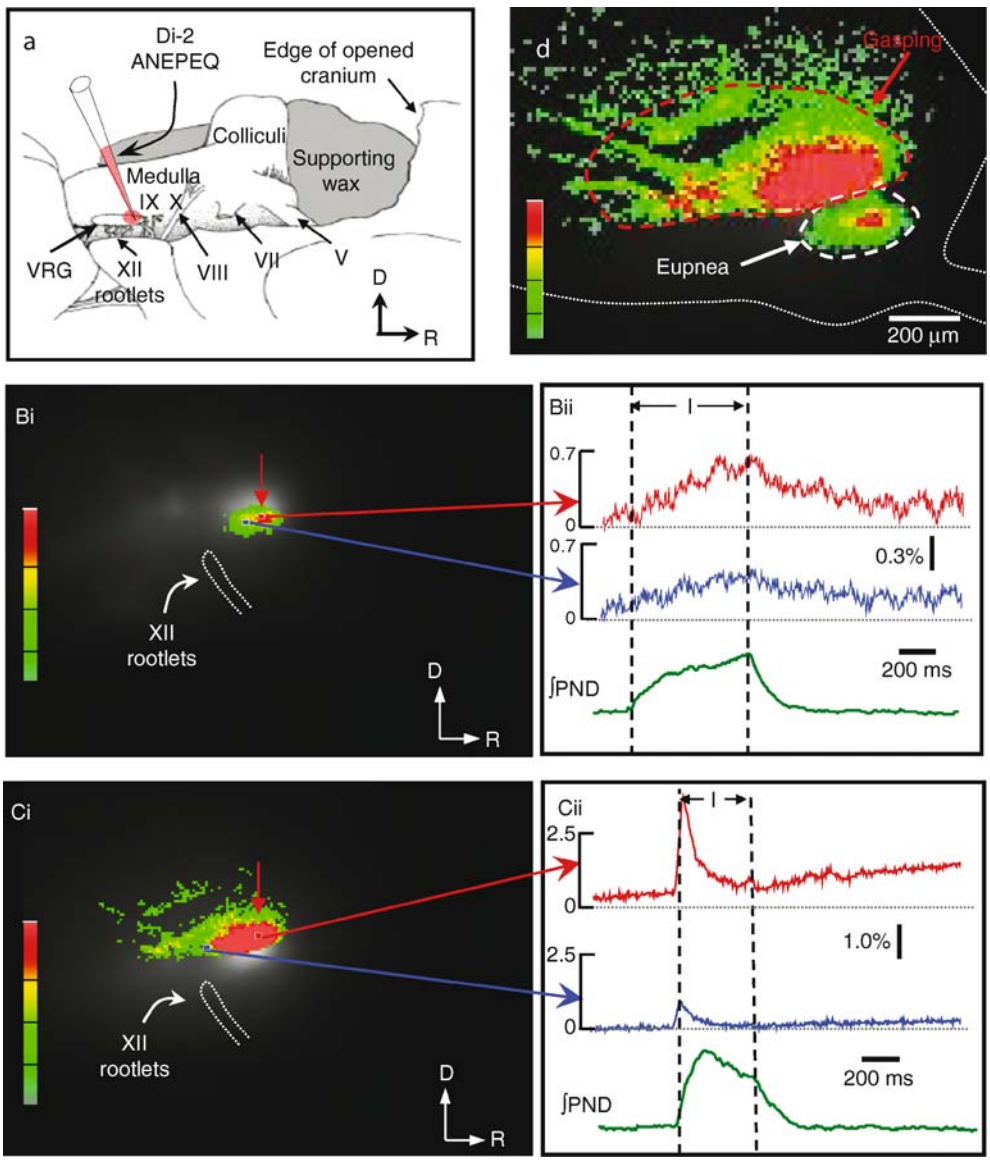
Imaging Central Respiratory Activity In Situ

With the robust and eupneic respiratory motor pattern generated by the WHBP, the preparation has been adopted by multiple laboratories to understand neural mechanisms governing respiratory rhythm and pattern generation. In a recent study, a voltage sensitive dye was

used to image spontaneous respiratory activity from the pre-Bötzinger complex (Fig. 2) in the WHBP [10]. This was the first time that the adult mammalian central respiratory rhythm generator had been visualized during eupneic-like activity. The study unearthed the temporal and spatial organization of neural circuitry employed during eupneic- and ►gasp- like respiration which led to the conclusion that there was a significant difference in the spatial organization of the gasp relative to the region exhibiting eupnea.

A Perspective for In Situ

For the future, a new direction for the WHBP will be to image single functionally identified cardiorespiratory



Central Integration of Cardiovascular and Respiratory Activity Studied In Situ. Figure 2 Imaging brainstem respiratory network activity during eupnea and gasping in situ. Using the WHBP, we exposed the lateral edge of the medulla oblongata and injected a voltage-sensitive dye (Di-2 ANEPEQ) into the Pre-Bötzinger complex (a). Using a fast CCD camera, we performed phrenic nerve discharge (PND) triggered imaging of respiratory activity during eupnea (b) and hypoxic-induced gasping (c). Temporal and spatial patterns of activity were compared (d) and indicated distinct sites for the genesis of eupneic- and gasp- like respiratory patterns. The vertical colored scale indicates degree of depolarization with red being greatest. Abbreviations: *D*, dorsal; *R*, rostra; *VRG*, ventral respiratory group; *V, VII, VIII, IX, X and XII* are all cranial roots; ∫, integrated. From [10], with permission.

Central Integration of Cardiovascular and Respiratory Activity Studied In Situ. Figure 3 The future in situ. A future challenge would be to image neurons within an intact functional brainstem using multi-photon microscopy. Such a system equipped with a physiological recording rig and perfusion circuit for a WHBP is shown in (a). Using a custom designed stage it is possible to mount a WHBP beneath the objective turret of a two-photon microscope giving the potential to image brainstem cardiovascular and respiratory neurons (b).

neurons using two-photon imaging (Fig. 3). This may be possible because the brainstem is mechanically stable and overlying superficial structures of the brainstem can be trimmed off to expose underlying cardiovascular and respiratory brainstem regions. Such an approach would allow unprecedented analysis of somatic and dendritic intracellular calcium fluxes and synaptic integration under different physiological and pathophysiological conditions (i.e., hypoxic (►hypoxia) driven gasping) on physiologically characterized neurons.

Acknowledgements

I would like to thank all colleagues who have worked with me on the in situ preparations for their interest, enthusiasm and great fun. My thanks to Professor David Williams and Dr Andrew Allen at the Department of Physiology, University of Melbourne, Australia for assisting with a two photon study. I am in debt to the British Heart Foundation for their generous financial support. I also acknowledge the Royal Society from whom a Royal Society Wolfson Research Merit Award was gleaned.

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Central Lobule

Synonyms

Lobulus centralis; Central lobule

Definition

The central lobule forms the ventral, upper segment of the vermis cerebelli and rests on the lingula of cerebellum and hence on the fourth ventricle.

Like the entire vermis cerebelli, the central lobule receives its afferents primarily from the spinal cord. It is part of the spinocerebellum – palaeocerebellum.

►Cerebellum

Central Medulla Oblongata Nucleus

Synonyms

Nucl. reticularis centralis; Central reticular nucleus

Definition

Belongs to the lateral reticular formation, i.e. to the parvocellular longitudinal zone of the RF, extending across the entire myelencephalon. Afferents come from the spinal cord, solitary tract, vestibular nuclei and the spinal nucleus of the trigeminal nerve. Efferents go to the gigantocellular reticular formation, the mesencephalic reticular formation as well as the bulbospinal tract in the intermediate substance of the spinal cord.

►Myelencephalon

Central Mesencephalic Reticular Formation – Role in Eye Movements

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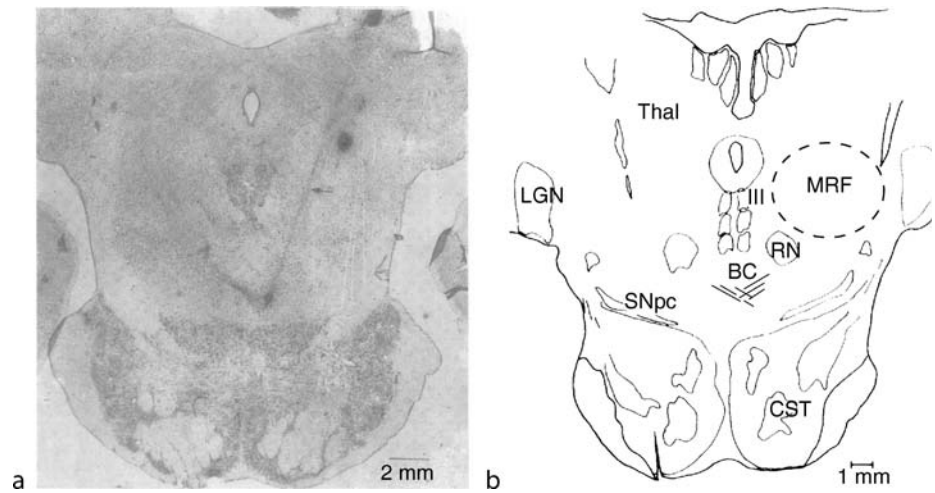
Definition

This article is focused on the role of the long lead burst neurons in the ►Mesencephalic reticular formation (MRF) in the control of gaze (i.e. combined head and eye movements). Anatomically, the MRF is located just ventral to the superior colliculus (SC) (see also ►Superior colliculus – role in eye movements), situated between the oculomotor nuclei medially and the lateral lemniscus laterally (Fig. 1).

The brachium conjunctivuum (i.e. crossing of the superior cerebellar peduncle) forms the caudal border, and the MRF extends rostrally through the core of the brain stem ending to the caudal portion of the thalamic



Central Mesencephalic Reticular Formation – Role in Eye Movements. Figure 1 Coronal sections through the midbrain and pons of a non-human primate (*Macaca mulatta*) showing the location of the MRF at caudal A3.5 (a) and rostral (A5.0) levels (b). A. Photomicrograph showing the location of an open movement field cMRF neuron (arrow). Dark region at bottom of the track is an electrolytic identifying lesion. B. Diagram at approximately A5.0 identifying the various structures surrounding the MRF in a monkey (dashed line surrounds the approximate area from which 12 MRF neurons were recorded). Abbreviations: *III*, oculomotor nuclei; *BC*, brachium conjunctivum; *CST*, cortico-spinal tracts; *LGN*, lateral geniculate nucleus; *MRF*, Mesencephalic Reticular Formation; *RN*, red nucleus; SN_{pc}, substantia nigra pars compacta; *Thal*, reticular nucleus of the thalamus.

reticular nucleus. Neurons in the cMRF not only receive collicular input, but form reciprocal connections that topographically target regions of the SC [1]. The cMRF also has strong, reciprocal projections to the omnipause region that gate saccades, the adjacent paramedian pontine reticular formation (PPRF) (see also ►Paramedian pontine reticular formation) [2] as well as descending direct and indirect projections (via the nucleus reticularis gigantocellularis, the putative premotor head movement region) to the cervical spinal cord. Ascending afferents to the cMRF arise from the fastigial nuclei of the cerebellum, the cervical spinal cord, and the PPRF itself [2]. These anatomic connections support the idea that cMRF neurons could assist in parceling the tectal outflow into separate eye and head channels (via PPRF and NRG) as well as mediating feedback to the SC about the current progress of gaze movements.

Characteristics

Lower Level Components

Three electrophysiological techniques have provided a better understanding of the organization of the cMRF and its role in gaze control: (i) electrical microstimulation; (ii) single unit recording; and (iii) reversible inactivation of the MRF in awake, behaving monkeys (Macaca mulatta). (For details of preparation and localization see [3]. All experiments have been carried out with the approval of the Animal Care and Use Committee of the University of Connecticut Health Center.

Electrical Micro-Stimulation of the MRF

Electrical microstimulation in the MRF of head-restrained monkeys has demonstrated that saccades with fixed amplitude and direction could be elicited from dorsal portions of the MRF, and saccades with variable amplitudes and directions – dependent upon initial eye position – could be elicited from the ventral MRF. Recent work has systematically examined the effects of initial eye position on the size and direction of the elicited saccade [4]. Stimulation in the dorsal portion of the cMRF of monkeys whose heads were both restrained and unrestrained confirmed and extended the earlier results. These experiments evoked saccades whose amplitude and direction remained constant and were thus initial eye position independent (i.e. "fixed vector"). However, stimulation in the more ventral portion of the cMRF elicited two types of variable amplitude saccades. One set of ventral sites evoked saccades in which the amplitude of the vertical and horizontal components varied with changes in initial eye position such that the eyes converged toward a goal in space. At many of these stimulation sites the choice of an initial eye position beyond the "goal" reversed saccade direction. Again this finding was confirmed with the head both restrained and unrestrained. This phenomenon became more pronounced with stimulation of the most caudal and ventral portions of the cMRF. At these locations, electrical stimulation generated "centering saccades" that brought the eyes from an eccentric location towards primary position.

Such centering movements have never been elicited from stimulation of the superior colliculus. In sum, electrical stimulation has suggested that the cMRF harbors a dorsal to ventral organization with respect to saccade amplitude and initial eye position.

Single Neuron Recording in the MRF

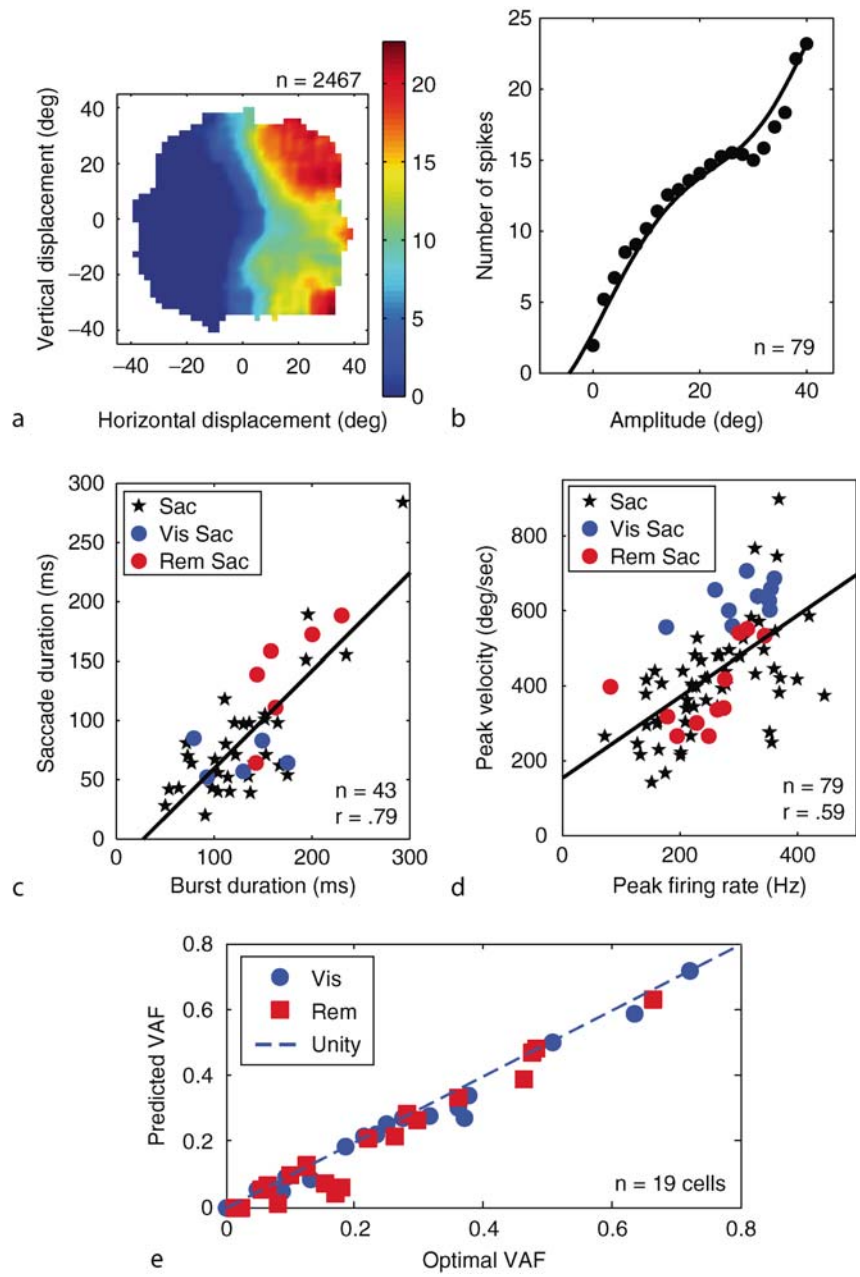
Single neuron recording has demonstrated two further subdivisions of the MRF. The neurons in the central portion of the MRF (the cMRF), located caudal to the posterior commissure discharge in association with horizontal eye movements [3], while MRF neurons located rostral to the posterior commissure are related to oblique saccades with larger vertical components [5]. Two major types of neurons have been identified in the cMRF. Neurons whose discharge started before saccades were called pre-saccadic, while neurons whose discharge began after saccade onset were called post-saccadic. The discharge of the pre-saccadic cMRF neurons began as an irregular, low rate of firing 100–125 ms before saccade onset. This prelude activity was then interrupted by a strong burst of activity that began 30 ms before saccade onset, qualifying these cells as long-lead burst neurons. The pre-saccadic group of cMRF neurons could be further subdivided into neurons with and without a high spontaneous level of activity upon which saccade associated changes in activity were superimposed. The high spontaneous level of activity of cMRF neurons was often inhibited before ipsilateral saccades. Similar to neurons in the superior colliculus, the cMRF pre-saccadic neurons discharge before a select group of contraversive saccades and thus had movement fields. However, the movement fields of cMRF pre-saccadic neurons were of three not the two types described in the SC. Like the SC, one sub-set of cMRF neurons had "closed movement fields" with a distinct distal border and they did not discharge for saccade amplitudes larger than the distal amplitude. A second group of cMRF neurons, again like those in the SC, had non-monotonic open movement fields and were very similar to the build-up neurons recorded in the superior colliculus (see also ►superior colliculus – role in eye movements). Thus, their discharge increased for saccade amplitudes up to an optimal beyond which larger amplitude movements were associated with equal or lower activity. Recent work in head unrestrained monkeys have shown that the cMRF harbors yet a third group of pre-saccadic neurons. Distinct from open-movement field neurons in the SC, the discharge of these monotonically open movement field, cMRF neurons continued to increase for movements up to the limit of measurement (approximately 70°), and were similar to the directional long-lead burst neurons found in the PPRF [6].

About 50% of the pre-saccadic cMRF discharged following the appearance of a visual stimulus, and thus had visual characteristics [3]. Like the movement associated discharge, the "visual" discharge was elicited for a select group of stimuli within the contralateral visual field. This visual receptive field was either the same or larger in size than the corresponding movement field. The visual response was typically phasic and was not maintained for the duration of the stimulus. When monkeys performed saccades to a previously flashed target the visual discharge would disappear and a second, movement associated burst would occur before a saccade to the remembered location of the target (a REM saccade). Evidence of this phasic discharge for REM saccades suggested that pre-saccadic cMRF neurons carried signals related to the execution of the upcoming saccade.

The idea that cMRF neurons participate in the generation of a *motor* signal used for saccade generation was supported by evidence that a phasic discharge occurred just before spontaneous or REM saccades made in total darkness. As a result, the discharge of cMRF neurons was not solely mediated by vision. At the same time, the peak discharge of cMRF neurons during visually guided (VG) saccades often exceeded by an order of magnitude the discharge during similarly sized spontaneous saccades made in darkness. Since visually guided saccades are often faster than spontaneous saccades generated in the dark, the increased response of cMRF neurons could have been the result of either a fusion of their visual and motor responses or a reflection of the velocity of the upcoming saccade [3]. However, in this earlier study, saccades of the same amplitude, but different velocities, were not directly compared.

One way to decide if cMRF neurons carried an independent temporal signal related to eye velocity was to directly compare their discharge during VG and REM saccades. If the REM and VG movements are closely matched for amplitude and direction, REM saccades are slower than their VG counterparts and thus a cell related to eye velocity should display a lower discharge. The neuron shown in Fig. 2 had a movement field with its highest discharge for saccades up and to the right (Red region of Fig. 2a).

If the spike number in the burst associated with all of the movements across a swath of the movement field within ± 7.5° of a line extending from fixation to the optimal discharge was plotted against amplitude there was a monotonic increase in the discharge up to 40° (the limit of measurement) (Fig. 2b). Furthermore, the majority of open-movement field (both monotonic and non-monotonic) cMRF neurons had a close correlation between burst and saccade duration (Fig. 2c, $r = 0.79$), as well as a tight correlation of peak discharge of the cell and peak eye velocity (Fig. 2d, $r = 0.59$). Based on these static measures, we hypothesized that the open movement field pre-saccadic cMRF neurons temporally encode eye velocity. To decide if this hypothesis was



Central Mesencephalic Reticular Formation – Role in Eye Movements. Figure 2 Analysis of a monotonically open movement field pre-saccadic cMRF neuron. (a) Movement field showing the spikes in the burst starting 30 ms before the saccade and ending with saccade offset. (b) Relationship of spike number to saccade amplitude across the movement field from primary position (straight ahead gaze) to the optimal discharge point for VG (Blue dot), (Red dots) and spontaneous saccades (Black stars). (c) Relationship of duration of the neuronal burst to the duration of the saccade for both VG (blue) and REM (red) saccades. (d) Relationship between the peak discharge of the neuron in the above analysis interval to the peak velocity of the saccade (VG data is blue, REM data is red) (e) Relationship between optimal VAF (Variance accounted for) and the predicted VAF. The optimal fit was determined by using either VG or REM data and relating firing rate, FR, to a scaled version of eye velocity. For example, for the VG data, the eye velocity model ($FR = a + b \times E_{VG}$) was used. The predicted FR for REM saccades was generated by using the same parameters (a and b) obtained from the VG fit and applying them to the velocity of the amplitude matched remembered saccades (i.e. $FR = a + b \times_{REM}$). The ratio of the VAF (predicted)/VAF (optimal) would be 1 if the prediction was precisely the same, and lower than one if the estimate using the VG saccades was weaker (blue dots). This process was also repeated using the REM saccades to predict the firing rate during VG saccades (red squares).

correct, we calculated the variance accounted for (VAF) using an eye velocity model using all saccades in the optimal direction. The accuracy of our prediction was assessed by taking the ratio of the VAF generated using the VG parameters, applied to the REM velocity, divided by the optimal VAF generated using just the REM saccades alone. The results for 22 cMRF neurons with monotonically open movement fields are shown in Fig. 2e. Note that when the VAF was 0.12 or higher, there was an excellent correlation between the predicted and optimal VAF. These findings strongly suggest that the increased discharge observed during visually guided saccades was the result of the increased velocity of the movements and NOT the combination of visual and motor responses.

A second major group of cMRF neurons, the post-saccadic neurons, has been discovered in monkeys free to move their heads. The discharge of these "post-saccadic" neurons began after the onset of gaze, would continue as long as the head was moving, but often ended just before the head stopped moving. No similar group of cMRF neurons has been identified when the head was restrained [3,5]. Like the pre-saccadic cMRF neurons, the post-saccadic neurons had movement fields, but spike number correlated most closely with increases in the amplitude of the head and not the gaze movement. A multiple regression analysis of the bursts of these neurons showed that the peak discharge of the majority of post-saccadic cMRF neurons was most closely associated with peak head velocity, with a small minority related to the end of the head movement. Similar to pre-saccadic neurons, the post-saccadic neurons discharged before gaze movements directed to the contralateral side. However, a significant minority discharged for head movements in both directions. A few of the post-saccadic neurons were also associated with vertical head movements. Analysis of the dynamics of the post-saccadic neuron discharge showed that a majority could not be modeled by scaled versions of head velocity. Moreover, the duration of their discharge was poorly correlated with the duration of either the accelerating or decelerating phase of the head movement. Additional experiments will be needed to further understand the role of these neurons in gaze control.

Higher Level Structures

Much of the human brain is devoted to acquiring visual information and then reorienting gaze (i.e. the combined movements of the head and eyes) to view targets of interest. The visual regions (e.g. V1, lateral geniculate nucleus, etc.) are organized topographically, such that neurons in a particular potion of the brain are only activated when a particular portion of the contralateral visual field is illuminated (see also Visual Cortex, connectivity and Visual Field Defects). This constitutes a spatial map: each individual neuron has a "visual receptive field". Once a target of interest activates such a receptive field, a series of steps ensue that they activate excitatory burst neurons in the paramedian pontine reticular formation (the PPRF) of the brain stem whose temporal pattern of discharge is closely associated with the force and speed of contraction required to move the muscles of the eyes (a temporal code) [6]. A similar area for control of head movement is thought to reside in the nucleus reticularis gigantocellularis (NRG) located at the ponto-medullary junction. The neuronal mechanisms necessary to convert topographically organized sensory information into the temporal pattern of activity required to carry out motor actions has been termed a spatial to temporal transformation (►spatial temporal transformation STT).

One locus in the brainstem where this STT may begin is in the superior colliculus (SC) of the midbrain (see also ►Superior colliculus – role in eye movements). In the primate SC, neurons in the intermediate and deep layers are topographically organized and are activated before a specific sub-set of contraversive head and eye movements (i.e. gaze) called a "movement field" (see also ►Superior colliculus – role in eye movements). As a result, the discharge of neurons in the intermediate and deep layers of the SC encodes the ►gaze displacement signal in retinotopic coordinates required to shift the fovea using a combination of head and eye movement to fixate the new visual target. Critical to understanding the current discussion is the observation that the temporal discharge pattern of an individual SC neuron is poorly correlated with the velocity of the upcoming saccade, and the duration of discharge is only moderately related to gaze duration [7]. The movement fields of SC neurons are either "closed" (i.e. activity abates for gaze shifts larger than an optimal amplitude) or "open" (i.e. spike number increases to a maximum and then begins to decline, but does not disappear for movements beyond the optimal amplitude) (see also ►Superior colliculus – role in eye movements). In other words, these open movement fields are "non-monotonic" with respect to amplitude. Thus, while neurons in the SC, especially those in the caudal portion of the SC, discharge for a wide range of gaze movements, their activity could not encode the temporal pattern required to precisely activate the muscles moving the eyes or head. This suggests that the tectal output must undergo further processing before being incorporated into the activity of the short-lead, excitatory burst neurons of the PPRF whose discharge profile is closely correlated with both saccade duration and velocity.

Function

A variety of techniques including electrical microstimulation, single neuron recording, and reversible inactivation, have demonstrated that neurons in the central Mesencephalic Reticular Formation (cMRF) participate

in the control of saccadic eye movements. Four neuronal sub-types have been identified. Evidence that the burst duration and peak discharge of pre-saccadic, monotonically increasing open movement field cMRF neurons were closely associated with saccade duration and peak velocity, respectively, suggested that these neurons were similar to the directional long-lead burst neurons found in the PPRF [6]. Since cMRF neurons have direct projections to the PPRF, they could be a critical component of an indirect tecto-reticular-pontine pathway that parallels the direct tecto-pontine pathways [6]. The close association of the directional long-lead burst neurons of the pons, and the monotonically increasing long-lead burst neurons of the MRF with saccade dynamics, supports a role for these neurons in the conversion of ►gaze signals coded spatially in the SC (i.e. movement fields organized topographically) into the temporal pattern of activity (i.e. rate of discharge) found in the excitatory burst neurons of the pons [8].

The precise role of the other neuronal sub-types in the cMRF remains unclear. For example, the physiological characteristics of cMRF neurons with non-monotonically open movement fields and neurons with closed movement fields were most similar to neurons located in the superior colliculus. The evidence of hypermetric saccades following the reversible inactivation of the caudal portion of the cMRF suggested that these two neuronal sub-types could participate in a feedback pathway that provided the SC with a signal of the current change in horizontal eye position [9]. However, a distinct feature of the non-monotonic open movement field neurons was the close association of their burst duration with saccade duration, particularly the horizontal component. This suggests an alterative idea that these neurons could feedback a saccade duration signal from the omnipause neurons to the SC [7]. By extension, MRF neurons located rostral to the posterior commissure could provide a feedback signal corresponding with either the current change or duration of the vertical component of eye movement to the SC. Finally, the physiological properties of the post-saccadic neurons are unique and may reflect aspects of either a feed-forward or feedback mechanism for controlling movements of the head. Future work will be directed to better understanding the different roles played by these other neurons in the control of gaze movements.

Pathology

Reversible Inactivation of the Neurons in the MRF

One question raised by the electrical stimulation and single neuron recording in the MRF was: What role do cMRF neurons play in the control of eye movement? Previous experiments had shown that electrolytic destruction of the MRF produced an ipsilateral gaze preference and a reduction in the speed of the slow phases of contralateral optokinetic nystagmus (OKN) [10]. The primary drawback of electrolytic lesions placed in the reticular formation was that they destroyed both cMRF neurons and fibers in passage, and may have encroached upon the ►nucleus of the optic tract associated with smooth pursuit eye movements (see also ►Smooth pursuit eye movements), which is located just above the cMRF. As a result, we injected the GABA-A agonist muscimol within the cMRF [4]. This agent selectively blocked neuronal activity leaving axons in passage unaffected. Three findings were evident following microinjections (0.5–1.5 μg) of muscimol placed at the location of previously recorded neurons in four monkeys. Injections caudal to the posterior commissure produced hypermetric, contralateral saccades and an instability in fixation (macro-saccadic square-wave jerks) [4]. There were two intriguing aspects to the injections in the MRF caudal to the posterior commissure (i.e. the cMRF). First, most of these injections generated a contralateral head tilt. Second, the hypermetria was most evident in oblique and vertical saccades. The horizontal component of oblique saccades was actually mildly hypometric while the vertical component was hypermetric. On the other hand, injections in the MRF rostral to the posterior commissure generated severe hypometria of the vertical component (both up and down) of oblique or vertical saccades. The horizontal component of oblique saccades was essentially unaffected by injections rostral to the posterior commissure. Taken in conjunction with single neuron recording [3,5] the results of inactivation support the view that the cMRF can be divided into two zones. The region caudal to the posterior commissure was most closely associated with the horizontal component of gaze shifts, and the portion rostral to the posterior commissure was most closely associated with the vertical component of saccades.

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Central Motor Conduction Time (CMCT)

Definition

The time needed for the evoked signals to pass from the motor cortex to spinal motoneurons along the corticospinal tract. Used as an indication of pathological processes affecting descending motor pathways and as a measure of their progress.

►Corticospinal Tract
►Motor Cortex – Output Properties and Organization
►Transcranial Magnetic Stimulation

Central Nervous Chemoreceptors and Respiratory Drive

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Synonyms

Central chemoreception

Definition

Central nervous chemoreception refers to the process by which changes in ►PCO_2 and pH within the central nervous system are detected and stimulate or inhibit ►respiration. Respiratory drive here refers to the endogenous stimulation of normal respiration that arises, in part, from central chemoreceptors.

Characteristics

Respiration

Respiration serves to exchange O_2 and CO_2 between body and atmosphere. The initiation and maintenance of respiration occurs in the brainstem and involves a network of ►respiratory neurons (see Respiratory Network Analysis). The amount of respiration depends on the response of this neuronal network to inhibitory and excitatory afferent input from peripheral and central sensors (see Respiratory Reflexes; Carotid Body Chemoreception and Respiratory Drive). Here we discuss central chemoreception.

Central Chemoreceptors: Locations and Cell Types

Central chemoreception was initially identified by the presence of respiratory responses to the perfusion of acidic fluids within the brain ventricles [1]. It was then localized to cells of unknown type at or beneath the ventral surface of the medulla oblongata by the direct application of acidic fluids [2]. But studies in vitro showed that neurons from many other locations within the hindbrain were responsive to pH changes see [3].

More recent experiments in vivo have provided support for the hypothesis that central chemoreception is a distributed property, i.e., that central chemoreceptor sites are widespread within the hindbrain [3–7]. In conscious animals, respiration is stimulated by the focal application of an acidic stimulus (increased CO_2) by reverse microdialysis at the (i ►retrotrapezoid nucleus [3], (ii) caudal aspect of the nucleus of the tractus solitarius [3], (iii) medullary raphe [3] (see Medullary Raphe Nuclei and Respiratory Control), and (iv) the fastigial nucleus of the cerebellum [4]. Similar studies in anesthetized animals also showed chemosensitivity at the locus ceruleus and the ►ventral respiratory group see [3]. Others have indicated the presence of chemoreception near the surface of the caudal ventral medulla as well [5].

In the retrotrapezoid nucleus, the chemosensitive neurons are glutamatergic and are identified by the presence of the vesicular glutamate transporter 2 (VGLUT2) see [3,7]. Their location is ventral to the caudal aspect of the facial nucleus just below one ventral medullary surface site at which earlier studies identified central chemoreception by application of acidic fluids [2]. The retrotrapezoid nucleus chemosensitive neurons express Phox2b, a gene associated with the development of the autonomic nervous system, and they also receive information arising in the peripheral chemoreceptors, the carotid bodies, via the nucleus of the tractus solitarius [7]. Inhibition or lesion of retrotrapezoid nucleus neurons diminishes the respiratory response to exogenously elevated CO_2 [3].

In the medullary raphe, the chemosensitive neurons are serotonergic [6]. They are located in the ventral medulla

with some being quite close to the ventral medullary surface. The blood supply to the medulla originates at the ventral surface and many chemosensitive serotonergic neurons are anatomically situated close to penetrating arteries. Inhibition or lesions of medullary raphe serotonergic neurons diminishes the respiratory response to exogenously elevated CO_2 [3]. (see Medullary Raphe Nuclei and Respiratory Control).

The chemosensitive neurons of the caudal part of the nucleus of the tractus solitarius, the fastigial nucleus of the cerebellum and the caudal ventral medulla have yet to be identified in terms of their cell type.

The chemosensitive neurons of the locus ceruleus are catecholaminergic see [3]. Their location is in the dorsal pons and they too are situated close to blood vessels. Lesions of locus ceruleus and other catecholaminergic neurons diminishe the respiratory response to exogenously elevated CO_2.

ATP release from cells of unknown type at the ventral medulla has also been postulated as involved in central chemoreception see [3].

Central chemoreception is a widely distributed property with many types of neurons involved. Each of the central chemoreceptor locations has known neuronal projections to the major groups of brainstem respiratory neurons.

Central Chemoreceptors: Function

The control of respiration, designed to maintain normal levels of arterial PO_2 and ►PCO_2, depends on constant feed-back from peripheral and central chemoreceptors. The peripheral chemoreceptors in the carotid body located at the bifurcation of the carotid artery detect and produce rapid respiratory responses to small changes in arterial PCO_2. They also respond to lowered arterial PO_2 levels but the magnitude of the response is small until arterial PO_2 is about 70 mm Hg (normal arterial PO_2 = 90 mm Hg). The central chemoreceptors are not directly affected by changes in PO_2. Their response to changes in PCO_2 is robust (~60% of the steady-state response to elevated CO_2 levels) but occurs more slowly than that of the carotid bodies [8,9]. These differences between central and peripheral chemoreceptors in response magnitude and dynamics indicate the presence of complex chemical-feedback system for CO_2 that governs respiration [8]. In order to maintain normal respiration, input from both receptors is necessary as lesions of either result in decreased respiration (and elevated arterial PCO_2 levels). Thus both contribute a drive to normal respiration. In contrast, sudden decreases in arterial PCO_2 can result in the cessation of breathing (apnea) if they occur in non-waking conditions. This hypocapnic apnea arises in the more rapidly responding peripheral chemoreceptors and is likely tempered by the slower central chemoreceptor response [8,9].

Central chemoreceptors are located within the parenchyma of the hindbrain. While some are situated quite close to arteries and vessels, in terms of overall function they are able to detect the pH of brain interstitial fluid [1]. In body fluids, CO_2 is in rapid equilibrium with water forming H_2CO_3 and then H^+ and HCO_3 ions. Thus a pH sensing mechanism can be responsive to both primary changes in PCO_2 and in pH. Brain interstitial fluid pH is determined by three interacting processes: (i the level of ►alveolar ventilation, which determines the arterial PCO_2, (ii) cerebral metabolic rate, which determines the rate of CO_2 production, and (iii) cerebral blood flow. For example, brain interstitial fluid can become more acidic and respiration stimulated if the alveolar ventilation is decreased, if metabolic CO_2 production is increased, or if cerebral blood flow is decreased, which would slow the clearance of tissue CO_2. Central chemoreceptors can be viewed as detecting a product, pH, of these three vital processes. Further, dysfunction of alveolar ventilation or cerebral blood flow such as to impair O_2 delivery to the brain would be detected as a change in interstitial fluid pH thus allowing central chemoreceptors to act as indirect sensors of cerebral oxygen delivery.

Central chemoreceptors, activated by brain interstitial fluid pH, provide a drive to breathe. They may also act as a "buffer" to modulate rapid responses that might arise from the peripheral chemoreceptors. There are many locations and cell types that are chemosensitive and the specific functions of each within the overall system design are not well understood. For example, different chemoreceptor sites can interact dramatically. Simultaneous inhibition of the retrotrapezoid nucleus and the medullary raphe produces a much greater inhibitory effect on the respiratory response to exogenously elevated CO_2 than does inhibition of either site alone [10].

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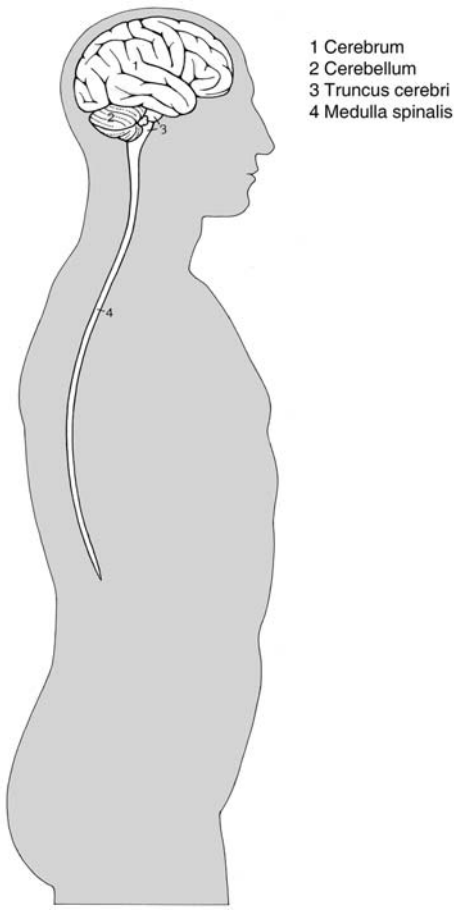
Central Nervous System (CNS)

Definition

The central nervous system (CNS) is a portion of the vertebrate nervous system consisting of the brain and spinal cord.



Central nervous system (CNS). Figure 1 The central nervous system in situ (1/6×). Original figure 01.01; taken from Nieuwenhuys, R; Voogd, J; van Huijzen, C. (Eds) 2008 "The Human Central Nervous System". Fourth Edition. Springer, Berlin. page 4 with permission.

Central Nervous System Degeneration Caused by Autoimmune Cytotoxic CD8+ T Cell Clones and Hybridomas

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Definition

►Theiler's murine encephalomyelitis virus (TMEV) infection of mice causes a demyelinating disease, which has similarities to ►multiple sclerosis (MS). Spleen cells from TMEV-infected SJL/J mice stimulated with antigen presenting cells (APCs) infected with TMEV resulted in a population of ►autoimmune $CD8^+$ cytotoxic ►T lymphocytes (CTLs) that killed not only TMEV infected but also uninfected syngeneic cells. We established $CD8^+$ CTL ►clones that kill both TMEV-infected and uninfected targets. Intracerebral injection of the clones into naïve mice induced central nervous system (CNS) degeneration. Using BWα-β-cells that lack T cell receptors (TCRs) as a fusion partner, we generated $CD8^+$ T cell hybridomas from the T cell clones. The T cell hybridomas produced interferon-γ (IFN-γ) when incubated with either infected or uninfected syngeneic target cells, which was blocked by CD8 or major histocompatibility complex (MHC) class I antibody. Our results indicate that $CD8^+$ T cells can recognize both a self antigen and a different viral protein. The T cell clones and hybridomas can be powerful tools to analyze TCR usage as well as CTL epitopes of viral and self antigens.

Characteristics

Historical and Technical Perspective on $CD8^+$ T Cell Versus antibody and $CD4^+$ T Cell Research

Although we do not know the exact mechanism by which the central nervous system (CNS) is damaged in

multiple sclerosis (MS), an example of a ►CNS demyelinating disease, ►viral CNS infection and immune responses have been suggested to play important roles in its pathogenesis. Historically, among the various effector mechanisms of the immune system, the antibody was first suggested as an effector molecule; this has been supported by findings, such as oligoclonal immunoglobulin G (IgG) bands in the cerebrospinal fluid (CSF) and demyelinating antibodies in organotypic cultures. Later, T cells were regarded as another candidate effector. The delay was partly because analyses of cellular immune responses were established after analyses of humoral immune responses [1]. Currently, many in the field consider MS to be a major histocompatibility complex (MHC) class II-restricted $CD4^+$ T helper 1 (Th1)-mediated disease, despite the observation that $CD8^+$ T cells have been found more frequently than $CD4^+$ T cells in demyelinating lesions of MS patients. This could reflect the technical feasibility of analyzing MHC class II-restricted $CD4^+$ Th cells *in vitro*, compared with that of MHC class I-restricted $CD8^+$ cytotoxic T lymphocytes (CTLs).

Endogenous antigens (usually made within the cells) are presented by MHC class I molecules, while exogenous antigens are presented by MHC class II molecules with a few exceptions [1]. Thus, if investigators add a protein of interest into cultures *in vitro* or inject protein into animals *in vivo*, protein in the extracellular space will be taken up by antigen presenting cells (APCs) and presented with MHC class II molecules, which enable detection of sensitized or stimulated $CD4^+$ T cells specific for the protein of interest. On the other hand, to stimulate $CD8^+$ T cells, a protein of interest needs to be expressed in the cytoplasm (in general) of APCs or target cells [1]. For this purpose, researchers usually either transfect APCs and target cells with cDNA encoding the particular protein or infect APCs and target cells with virus encoding the protein. In addition to the above technical difficulty stimulating $CD8^+$ T cells, there are storage and handling problems in $CD8^+$ T cell analyses. For instance, standard CTL assays have low throughput and require handling of chromium-51 (^{51}Cr) that decays by electron capture and gamma (γ) emission with a short half-life of 27.7 days, while standard helper T cell assays, to detect lymphoproliferative responses, have high throughput using 96-well microtiter plates and require tritiated (^3H)-thymidine that emits a weak beta (β) ray with a half life of 12.3 years. The ^{51}Cr release assay is still a standard assay to detect $CD8^+$ CTL responses, although several alternative detection methods have been introduced to detect $CD8^+$ T cell responses [1], such as flow cytometry with intracellular cytokine staining and lactate dehydrogenase (LDH) release assays.

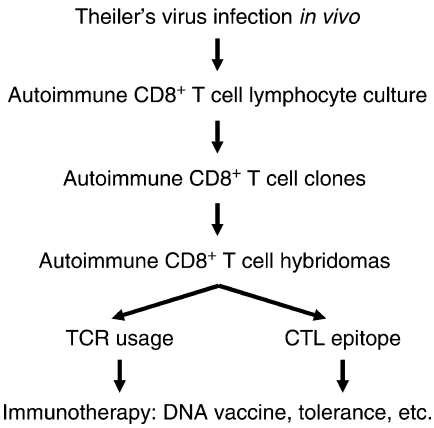
Theiler's Murine Encephalomyelitis Virus Infection

Various viruses have been found to induced demyelination in laboratory animals. One of the most studied experimental models is infection of mice with Theiler's murine encephalomyelitis virus (TMEV) [2]. TMEV belongs to the family ►*Picornaviridae*. Although the precise mechanism of demyelination is not known, several effector mechanisms have been demonstrated to play important roles, including direct oligodendrocyte infection, TMEV-specific antibody (reviewed in [2]), TMEV-specific $CD4^+$ Th1 cells, macrophages, apoptosis of oligodendrocytes and axonal damage [3].

We have demonstrated the generation of autoimmune $CD8^+$ CTLs that cross-react with both virus and autoantigen in TMEV infection. Here, we will describe the history and direction of our investigations into the autoimmune CTLs generated in TMEV infection: (i) discovery and characterization of autoimmune T cells in bulk lymphocyte culture derived from mice infected with TMEV; (ii) establishment and characterization of T cell clones; (iii) generation of T cell hybridomas; and (iv) T cell receptor (TCR) and CTL epitope analyses, which will provide useful information to elucidate its pathogenesis and to develop tailor-made immunotherapies such as DNA immunization and tolerance induction (Fig. 1).

Autoimmune $CD8^+$ T Cell in Bulk Lymphocyte Culture

$CD8^+$ CTLs have been suggested to play an important role in not only eradication of virus but also demyelination in TMEV infection. To explore the role of CTLs, we monitored CTL activity using a 5h ^{51}Cr release assay [4]. We utilized splenic mononuclear cells (MNCs) from SJL/J mice ($H\text{-}2^s$) infected with the Daniels (DA) strain of TMEV as effector cells and a syngeneic fibroblast cell line, PSJLSV (PSJL, $H\text{-}2^s$), as target cells. We stimulated the MNCs with TMEV-infected APCs for 1 week *in vitro*, and used these stimulated cells as effector cells in CTL assays. To our surprise, the MNCs killed not only TMEV-infected PSJL, but also uninfected PSJL (syngeneic or autoimmune killing). The autoimmune CTLs showed the highest killing against syngeneic target cells, intermediate killing against F1 target cells ($H\text{-}2^{b/s}$), and low killing against allogeneic target cells ($H\text{-}2^b$). The phenotype of the CTLs was $CD3^+/CD4^-/CD8^+$. The autoimmune killing required cell-to-cell contact and was mediated by the Fas-FasL pathway, not by the perforin pathway. Killing was associated with interferon (IFN)-γ production in enzyme linked immunospot (ELISPOT) assays [5]. The CTLs were efficiently induced by vaccinia virus (VV) encoding the DA virus capsid proteins, but not by APCs infected with GDVII virus, a non-demyelinating strain of TMEV. Injection of the CTLs into the brain of naïve mice caused meningitis and perivascular cuffing, not only in the brain parenchyma, but also in the spinal cord distant from the injection site.



Central Nervous System Degeneration Caused by Autoimmune Cytotoxic CD8+ T Cell Clones and Hybridomas. Figure 1 From mice infected with TMEV, we detected autoimmune CD8+ T cells that kill both uninfected and TMEV-infected syngeneic target cells. To characterize the autoimmune CTLs induced following TMEV infection, it was necessary to establish long-term T cell lines and clones. To maintain cytotoxicity, supplementation with interleukin (IL)-2 was necessary except during the first week of *in vitro* stimulation with TMEV-infected APCs. From the T cell clones, we established autoimmune CD8+ T cell hybridomas. Unlike the T cell clones, the T cell hybridomas can be grown and expanded without the addition of APCs or exogenous IL-2. We found that CD8+ T cell clones and hybridomas can recognize both a self antigen and a viral protein. Determination of TCR Vβ and CDR3 spectratyping of TMEV-specific T cell hybridomas, clones and uncloned bulk autoimmune T cell cultures will allow us to attempt modulation of TMEV infection by treating mice with Vβ antibodies or by vaccination with cDNA encoding TCR Vβ. Our novel experimental findings and approach can be applicable to elucidation of involvement of CD8+ CTLs in immune-mediated diseases, including MS, where CD8+ T cells have been demonstrated in demyelinating lesions. Analyses of TCR usage and CTL epitopes of viral and self antigen will provide useful information to elucidate its pathogenesis and to develop tailor-made immunotherapy such as DNA immunization and tolerance induction. This will extend the studies of several other groups where autoreactive CD4+ T cells have been described as containing degenerate TCRs that can recognize both autoantigen and microbial peptides. Since CD4+ T cells have been reported to recognize both self and microbial antigens from MS patients, similar autoreactive CD8+ CTLs could also contribute to the pathogenesis in MS and other virus infections.

Autoimmune CD8+ T Cell Clone

By limiting dilution, we established CD3+/CD4−/CD8+ CTL clones [6]. The CTL clones showed MHC class I-restricted killing of both TMEV-infected and uninfected syngeneic target cells, although infected target cells were killed more efficiently. Intracerebral (i.c.) injection of the clones into naïve mice induced large CNS degenerative lesions with loss of myelin and oligodendrocyte apoptosis. In contrast, we did not see degenerative lesions in mice injected with control CD8+ T cells activated with concanavalin A (ConA) or CD8+ enriched lymphokine-activated killer (LAK) cells.

Autoimmune CD8+ T Cell Hybridoma

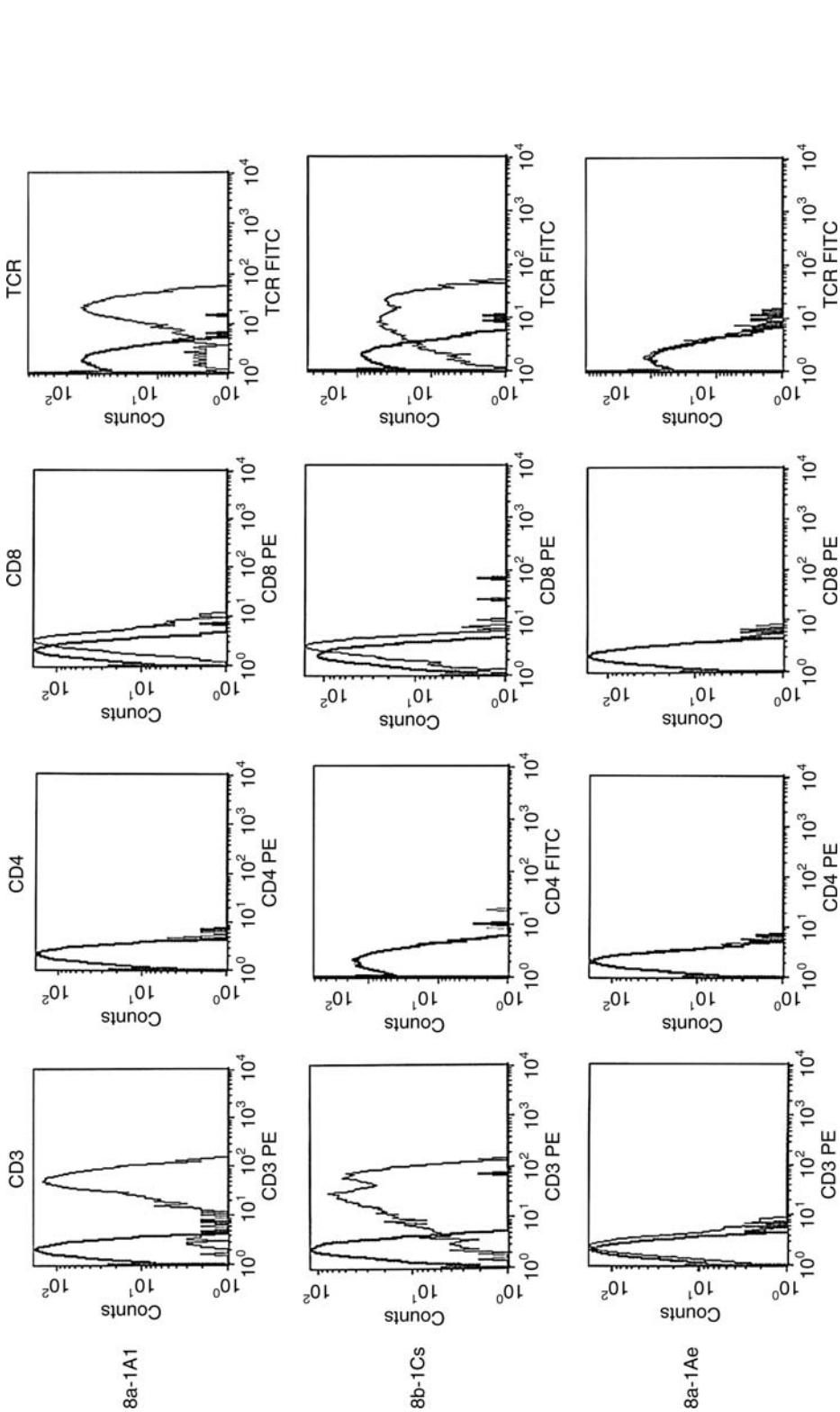
In most CTL assays, T cells mediate killing through direct lysis. For example, in Fas-mediated killing, APCs present antigen to and thereby activate CTLs. This leads to up-regulation of FasL on CTLs, enabling the CTLs to kill the APCs positive for Fas. But in rare instances, CTLs have been shown to mediate killing through bystander lysis, where the APCs present antigen to and activate CTLs, inducing expression of FasL, but the target is a third Fas-positive cell that lacks the appropriate MHC restriction or antigen presentation. Here, the FasL-positive CTLs recognize the antigen presented by MHC molecules on the APCs, and the CTLs kill Fas-positive target cells without the trimolecular interaction of TCR with antigen and MHC molecules on the target cells.

In our system, uncloned splenic populations and T cell clones contain APCs [6]. After the 1 week *in vitro* culture of bulk T cells with TMEV-infected APCs, live cell populations were separated by a density gradient and used as effector cells in CTL assays. Here, the effector cells consisted mainly of TMEV-specific T cells, since the majority of other cell types were not able to survive after 1 week in culture. However, we cannot rule out the possibility of the existence of small numbers of live TMEV-infected APCs mixed in among the effector cell populations. Thus, this raised the question that the killing by splenic bulk culture or CTL clones might be due to bystander killing of the target, not by direct lysis of the target. To rule out this possibility, we developed T cell hybridomas having similar specificities and properties to those of the T cell clones.

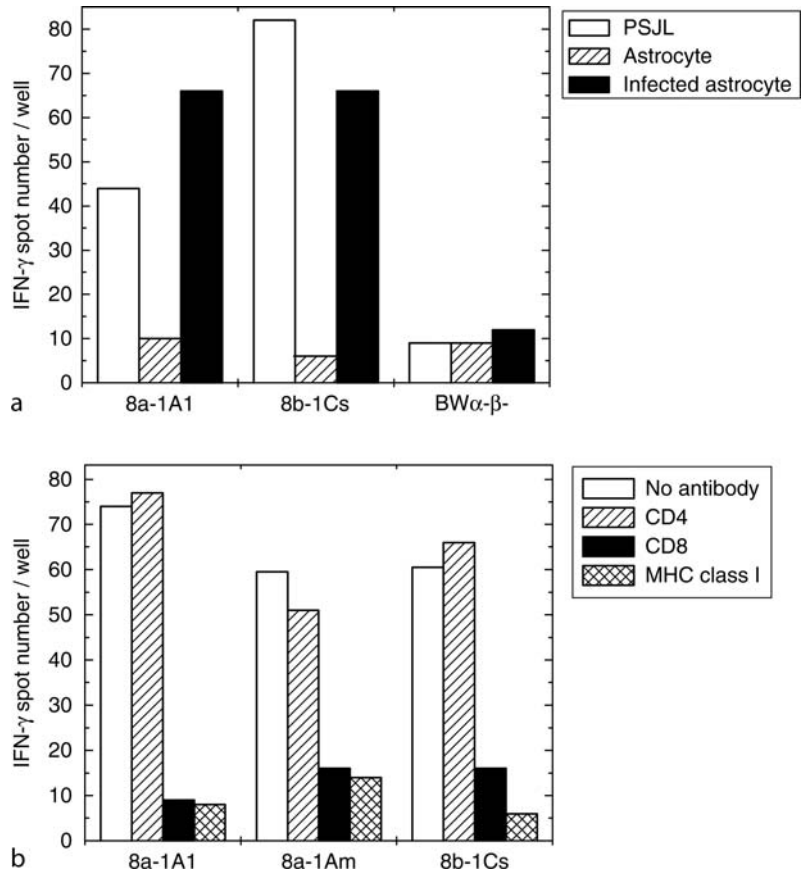
All T cell hybridomas were CD4− (Fig. 2). The majority of clones were also TCR+, although three hybridomas were TCR−. Some hybridomas express low levels of ►CD8 antigen, while others were CD8−. Hybridomas produced IFN-γ when incubated with infected or uninfected PSJL cells and TMEV-infected astrocytes but not uninfected astrocytes (Fig. 3a). The IFN-γ production was inhibited by the addition of CD8 and MHC class I antibodies to the cultures, but not by addition of CD4 antibody (Fig. 3b). I.c. injection of some hybridomas resulted in CNS pathology characterized by parenchymal and perivascular cell infiltration and gliosis (Fig. 4).

Characterization of TCR

One of the characteristics of organ-specific ►autoimmune disease is that the development of the disease is



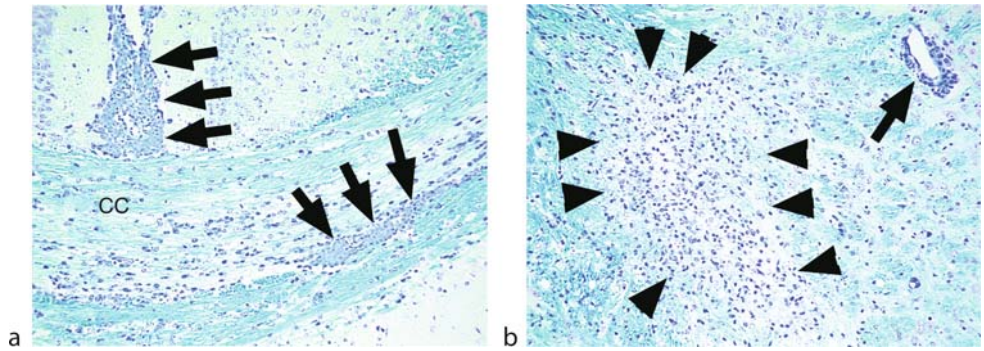
Central Nervous System Degeneration Caused by Autoimmune Cytotoxic CD8+ T Cell Clones and Hybridomas. Figure 2 We generated the autoimmune T cell hybridomas, using TMEV autoimmune $CD8^+$ CTL clone cells, 8a-1A or 8b-1C, with the BWα-β- (BW-1100.129.237) cell line that lacks the α and β chains of the TCR. Using flow cytometry, we characterized the T cell hybridomas according to surface antigens. T cell hybridomas were tested for surface markers by using monoclonal antibodies directed against CD4, CD8 and TCR. The surface phenotype of TMEV-induced autoimmune T cell hybridomas was $CD3^+$ $CD4^-$ $CD8^{dim}$ TCR^+ (8a-1A1, *top* and 8b-1Cs, *middle*) or $CD3^{dim}$ $CD4^-$ $CD8^-$ TCR^- (8a-1Ae, *bottom*). CD8 may be preferentially down-regulated during prolonged *in vitro* culture or fusion, because the parent T cell clones were originally highly positive for CD8. FITC, fluorescein isothiocyanate. PE, phycoerythrin.



Central Nervous System Degeneration Caused by Autoimmune Cytotoxic CD8+ T Cell Clones and Hybridomas. Figure 3 TMEV-induced T cell hybridomas were tested for IFN-γ production, using an ELISPOT assay. Hybridomas (8a-1A1, 8a-1Am, 8b-1C, or the fusion partner (BWα-β-) were used as effector cells. Uninfected PSJL, astrocytes, or infected astrocytes (multiplicity of infection = 20) were used as target cells. A concentration of 1×10^5 cells/well of effector cells were incubated overnight with target cells at an effector/target (E/T) ratio of 1:1. (a) TMEV-induced hybridomas, 8a-1A1 and 8b-1Cs, produced IFN-γ when cultured with uninfected PSJL (PSJL, *open*) and infected astrocytes (*closed*), but not with uninfected astrocytes (Astrocyte, *hatched*). BWα-β- cells did not produce IFN-γ. (b) TMEV-induced CD8+ T cell hybridomas were incubated with uninfected PSJL in the absence (No antibody, *open*), or presence of antibody against CD4 (*hatched*), CD8 (*closed*), or MHC class I (*cross hatched*). CD8 and MHC class I, but not CD4, antibodies blocked the IFN-γ production.

closely associated with, or induced by, a particular type of T cell reactive to organ-specific antigens [7]. Thus, it has been postulated that autoantigen-reactive T cells bearing particular types of TCRs are expanded clonally during the course of the disease. Based on limited usage of the TCR repertoire in some types of experimental autoimmune encephalomyelitis, a particular single TCR has been suggested to be involved in encephalitogenicity (V-region disease hypothesis). More recently, to identify TCRs expressed on clonally expanded T cells, there are at least three types of analysis: complementarity determining region (CDR) 3 spectratyping, single-stranded conformational polymorphism (SSCP) and heteroduplex analysis [7]. CDR3 is encoded by the V(D)J junctional sequences and may directly contact the MHC-bound peptide, thus conferring T cell specificity for a particular peptide-MHC complex (CDR1 and 2 are encoded by germline and allow the TCR to interact with the α helices of the MHC molecule). In SSCP and heteroduplex analyses, each band on the gel represents expansion of a particular single TCR clone. In contrast, each band demonstrated in CDR3 spectratyping simply represents those TCRs with a CDR3 region of the same size. Therefore, the nucleotide sequence of the CDR3 region of the TCR clones derived from expanded bands should be determined to confirm the presence of clonal expansion in the bands [8].

TCR usages and CDR3 spectratyping are the methods that show TCRs of oligoclonally expanded T cells, compared with control samples. The methods do not require knowledge of putative autoantigens that are not known in most autoimmune diseases, including MS. Nucleotide and amino acid sequences of the CDR3 region of the TCR clones derived from the spectratypes



Central Nervous System Degeneration Caused by Autoimmune Cytotoxic CD8+ T Cell Clones and Hybridomas. Figure 4 We investigated whether T cell hybridomas could induce CNS pathology. We inoculated 1 × 10^6 T hybridoma cells, 8a-1Ae (a) and 8b-1C5 (b) into the right cerebral hemisphere of naïve SJL/J mice. CNS histology was examined 1 week after inoculation. Mice receiving T cell hybridomas developed different pathology depending on the T cell hybridoma lines. Some hybridoma lines stayed only in the meningeal spaces, while others infiltrated into the parenchyma, including the corpus callosum (CC) (Fig. 4a, *arrow*) and the internal capsule, and spinal cord nerve roots, which were distant from the injection site. (b) Gliosis (*arrowhead*) and perivascular cell infiltration (*arrow*) were seen in the internal capsule. However, we did not see large white matter degenerative lesions, comparable to those observed in mice injected with TMEV-induced autoimmune CD8+ T cell clones. Mice receiving BWα-β- cells (fusion partner) had only meningeal cell infiltrates. Luxol fast blue stain. Magnification, ×84.

of interest can be used to determine whether there is a clonal expansion and whether specific CDR3 motifs are used or not. For example, Matsumoto and colleagues [9] found that the Vβ5.2 spectratype is expanded more frequently than other Vβs in MS patients, suggesting that the finding provides useful information for designing TCR-based immunotherapy in MS. Thus, information on the identified pathogenic TCRs can be used in the prognosis of the disease or future treatment using antibodies and DNA vaccination against TCRs.

It is controversial whether specific TCR Vβ or CDR3 motifs are used in TMEV infection; some reports support specific TCR usage and others do not. We attempted to determine TCR usage by TMEV-induced $CD8^+$ T cell hybridomas, using flow cytometry with a mouse Vβ TCR screening panel, containing monoclonal antibodies against Vβ 2, 3, 4, 5.1, 5.2, 6, 7, 8.1, 8.2, 8.3, 9, 10^b, 11, 12, 13, 14, and 17^a TCR. We found that hybridoma, 8a-1A1, was positive for TCR Vβ3 and 8b-1Cs was negative for all antibodies included in the panel. TCR Vβ region gene sequence analyses also showed the presence of Vβ3 in 8a-1A1 (Table 1).

Defining the Viral Epitope and Self Antigen

There are several methods currently employed for identifying antigens recognized by CTLs: (i) molecular biology approaches using cDNA libraries from a microbe or tissue of interest [10]; (ii) direct acid elution and amino acid sequence analysis of MHC-associated peptides; (iii) epitope mapping conducted with a series of overlapping peptides in cases where the antigenic protein is known; (iv) the use of algorithms that employ known MHC binding motifs for epitope predictions within a protein of interest; and (v) synthetic combinatorial libraries that do not require knowledge about T cell specificity or MHC restriction. Of these methods, expression cloning of cDNA libraries and peptide elution have been the preferred methods to identify antigens recognized by T cells for which no molecular information is available. ELISPOT assays have improved the sensitivity and efficiency of T cell antigen cloning from cDNA expression libraries [10].

We have developed T cell hybridomas that are easy to grow and produce IFN-γ in ELISPOT assays in response to TMEV-infected or uninfected PSJL, or infected astrocytes but not uninfected astrocytes. These T cell hybridomas can be used to define the viral epitope as well as the self epitope that is recognized by the cross-reactive TCR. We are using astrocytes transfected with a pCMV vector encoding each of the viral capsid proteins, VP1, 2, 3, and 4 [2] as well as the P2 or P3 regions of the TMEV genome encoding nonstructural proteins [2]. We will use a similar approach to identify what cellular antigen(s) is recognized by the TMEV-induced autoimmune CTL by transfecting astrocytes with an expression library constructed from the CNS of SJL/J mice. Once the protein is identified, either deletion mapping or overlapping peptides can be used to identify the self epitope. If it is a cell-specific protein found only in oligodendrocytes, then one could predict that direct killing of the oligodendrocyte would be a plausible mechanism for the demyelination. *In vivo* roles of TMEV-induced autoimmune CTLs can be clarified by sensitization of TMEV-infected or uninfected mice with (i) the CTL epitope peptide (or its altered ligand) of TMEV and autoantigen, emulsified in complete Freund's adjuvant (disease induction and exacerbation) or in incomplete Freund's adjuvant

Central Nervous System Degeneration Caused by Autoimmune Cytotoxic CD8$^+$ T Cell Clones and Hybridomas.

Table 1 TCR Vβ chain gene segment usage in TMEV specific hybridomas[a]

	CDR3[b]		
	Vβ3	Dβ1/N[c]	Jβ2.1
8a-1A1	GCAGTC	AGGG/ACAG	AACTAT
8b-1Cs	ND[d]	ND[d]	ND
BWα-β-	ND	ND[d]	ND

[a]We tested 8a-1A1 and 8b-1Cs for the presence of Vβ3 in their TCRβ chain by means of reverse transcription (RT)-PCR and sequencing. BWα-β- cells were tested as a negative control. Primers used to amplify the TCR Vβ region gene sequences were as follows: Vβ3, 5′ GGCTACAAGGCTCCTCTGTTAC 3′, which is specific for the Vβ3 gene and Cβ, 5′ GACAGGTTTGGGTGAGCCCTCTGG 3′, which is specific for the constant region and was used for RT and PCR. Appropriately sized bands were isolated from agarose gels, and the band-isolated PCR products were sequenced. TCR Vβ region gene sequences were compared with those in the GenBank database using the BLAST sequence alignment program.
[b]CDR3; complementarity determining region 3.
[c]N, non-templated nucleotide insertions.
[d]ND, not detected.

(treatment or tolerance induction); (ii) recombinant VV; or (iii) cDNA encoding the epitope. Induction of the CTLs that recognize both virus and autoantigen can result in viral clearance in the CNS of mice infected with TMEV, while the CTL induction in uninfected mice can lead to CNS degeneration.

Acknowledgments

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Central Nervous System Disease – Natural Neuroprotective Agents as Therapeutics

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Synonyms

Neuroinflammatory brain disorders; Pro-inflammatory mediators; Herbal neuroprotectives

Definition

Pro-inflammatory mediators in disorders of the central nervous system and potential neuroprotective agents of natural origin.

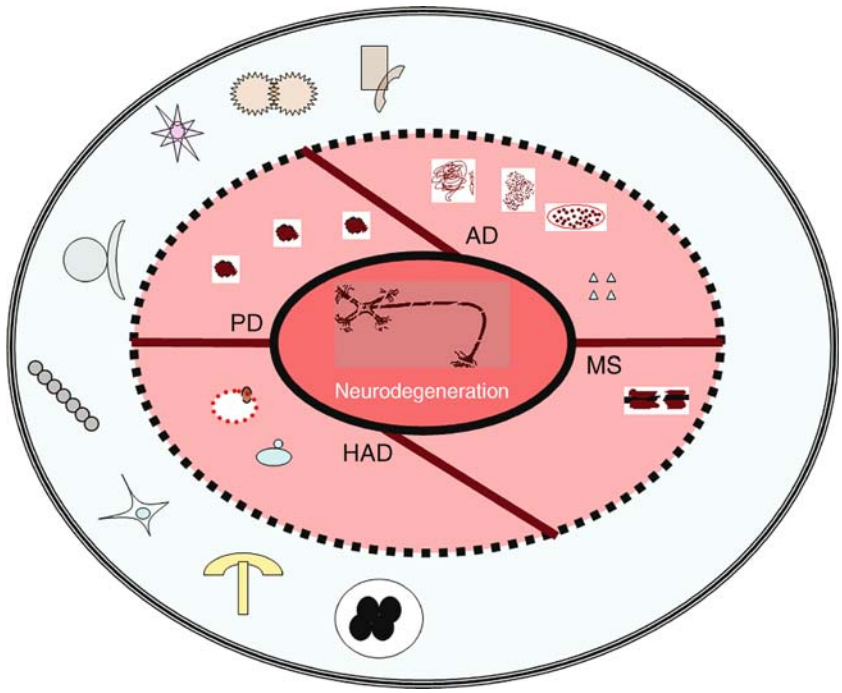
Characteristics

Pathology

Disorders of the central nervous system (CNS) cover a wide range of diseases from depression, Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), ►HIV-associated dementia (HAD) and viral encephalopathies. However, ►non-steroidal anti-inflammatory drugs (NSAIDs) currently available on the market are not as effective as originally anticipated. Furthermore, side effects associated with long term use of these medicines discourage their use in chronic CNS pathologies. In order to develop effective treatment strategies, insight into the molecular basis of these disorders is essential. The complexity of the brain architecture, its components and neurocircuitry has made this task immensely challenging. The advent of rapidly evolving technology has enabled us to understand the common hallmarks of the pathophysiology of most of these disorders. The root cause in each one of them may differ from the other, but all of them show the involvement of inflammatory responses initiated by cells of the immune system in the brain. In the current essay, the primary factors involved in the etiologies of AD and HAD are described, and both primary and secondary factors contributing towards ►neuroinflammation (Autoimmune, Chronic) in major CNS disorders are summarized in Fig. 1.

AD

AD is characterized by the presence of ►amyloid plaques, ►amyloid β protein, and neurofibrillary tangles (NFT). The role of these proteins in the pathogenesis of AD is described in detail in many reviews, consequently it is briefly summarized in this essay. The reader is referred to a descriptive review by J Haddad [1] where the role of pathogenic proteins involved in the etiology of AD such as ►amyloid protein, tau, and the importance of mitogen-activated protein kinases (MAP kinases) in their processing is discussed. As mentioned in this review, the amyloid plaques develope due to altered metabolism of



Central Nervous System Disease – Natural Neuroprotective Agents as Therapeutics. Figure 1 The primary and secondary factors involved in the etiology of major neurodegenerative disorders of the brain (AD, PD, HAD and MS) are outlined in this figure. The primary factors (Lewy body, Aβ peptide, diffuse plaques, well defined amyloid plaques, neurofibrillary tangles, demyelinated neurons, HIV with gp41, and Nef are shown in the inner dotted eclipse. The secondary pro-inflammatory mediators, the complement system, activated microglia. T cells, macrophages, COX enzymes, astrocytes, free radicals, and NF-κB are shown in the outer eclipse. The neurodegeneration due to these factors is symbolised by a cartoon of damaged neuron in the centre.

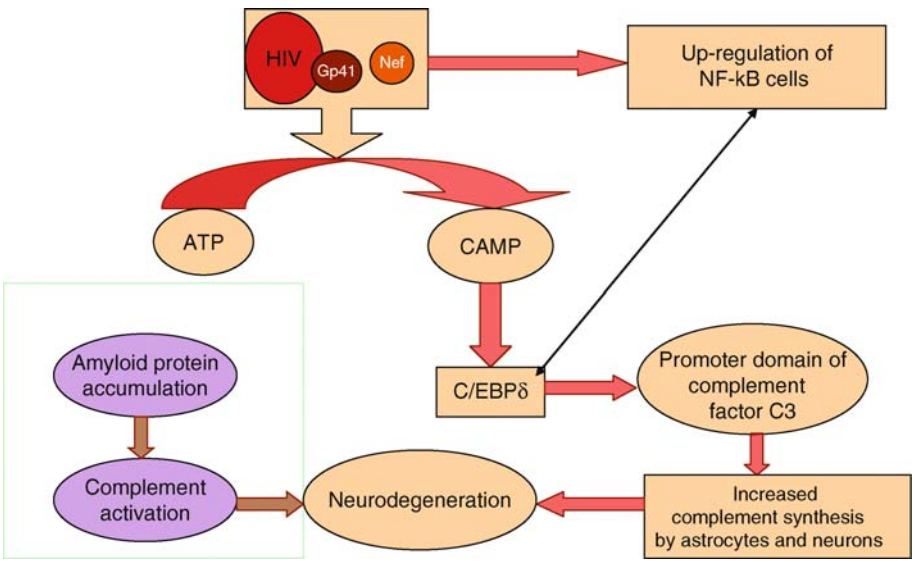
►amyloid precursor protein (APP). Mutations in APP, Presenilin (PSEN1 and PSEN2) genes lead to the formation of Aβ peptides and plaques, and phosphorylation is an important mechanism for the formation of plaques. In AD, there is also hyperphosphorylation of tau protein. MAP kinases play an important role in the phosphorylation of these proteins. All these factors contribute towards the primary pathogenesis of AD.

HAD

Both viral and host factors contribute to the neuropathophysiology of HAD. The HIV envelope protein gp120 plays an important role in the pathophysiology of the virus. This protein undergoes structural arrangement before binding CD4, and therefore escapes the antibody response. In a recent study by T Zhou et al., the structural analysis of gp120 stabilized in CD4 binding site and bound to a broadly neutralizing antibody b12 revealed that the antigenic epitopes are conserved in gp120 [2]. This is an important therapeutic target for the development of neutralizing antibodies against the HIV envelope to reduce the viral load and thereby reducing the neurological symptoms associated with AIDS. The other HIV proteins which play an important role in the HIV mediated neurodegeneration are ►Nef and ►gp41. These proteins induce activation of ►the complement system through their direct actions on the promoter of the C3 component of the complement system. This results in the up-regulation of the complement system ultimately leading to neuroinflammation [3]. The recent evidence suggests that there is deposition of amyloid protein in the brain of HIV positive patients [4]. The pathogenesis in HAD with the focus on complement up-regulation is shown in Fig. 2.

Common Pro-Inflammatory Mediators

Although, the primary etiologies of CNS disorders affecting a large sector of populations worldwide differ from each other, most of them show an activation of the immune system and the involvement of common pro-inflammatory mediators (►pro-inflammatory cytokines). The activation of cells of the immune system and ►residual brain cells, although beneficial initially, results in the release and/or activation of several pro-inflammatory mediators, which are responsible for damage to the brain tissue. Activation of ►astrocytes and ►microglia can be found in most of the brain disorders. The common pro-inflammatory mediators found in most of the neurodegenerative disorders such as AD, PD and HAD are free radicals, ►NF-κB, cyclooxygenases (COX-2), and most importantly, the complement system. Several studies have shown



Central Nervous System Disease – Natural Neuroprotective Agents as Therapeutics. Figure 2 Activation of the complement system by HIV, and its pathogenic proteins.The speculations from Cornelia Bruder et al., [3] and the finding that circulating monocytes and macrophages in the brain of HIV infected patient express APP as well as diffuse plaques [4] are combined in this figure. As shown in the figure, HIV and its pathogenic proteins Nef and gp41 activate the transcription factor C/EBPδ. The activated transcription factor can simultaneously bind to NF-kB and C3 promoter. Activation of NF-kB increases viral replication, and simultaneous binding to C3 promoter lead to increased expression of C3 complement component and subsequent neuroinflammation. Also, the diffuse amyloid plaques and increased APP expression by circulating monocytes and brain macrophages of HIV infected patient may lead to the activation of the complement system, a major pro-inflammatory mediator responsible for neurodegeneration.

the involvement of COX-2 in HAD. Many theories have been suggested for the induction of COX-2 in HIV mediated neuroinflammation. According to one theory, HIV-1-infected monocyte derived macrophages interact with the brain endothelium and this leads to the induction of COX-2 in the brain. Induction of COX-2 in the brain of HIV infected patients could be one of the major neuroinflammatory event mediated by HIV [5]. The common pro-inflammatory mediators and the role of the complement system in disorders of the CNS have been reviewed by many including Kulkarni et al., 2004 [6].

The two major disorders of concern with no effective treatment are AD and HAD. Although, their root causes differ from each other, both of them show altered APP metabolism leading to amyloid formation. It is well established that the amyloid plaques are responsible for the activation of pro-inflammatory mediators including the complement system in AD. Thus, amyloid deposition found in HIV positive patients might also be responsible for the activation of the complement system. Recently, it was found that both HIV and its pathogenic proteins are responsible for up-regulation of the complement system [3]. Here, activation of microglia and other cells of the immune system is also evident. The other disorders with similar up-regulation of the complement system and aforementioned pro-inflammatory mediators affecting the majority of the World's population are MS, scrapie and PD. Thus, pro-inflammatory mediators including complement components could be regarded as common therapeutic targets in the treatment and prevention of these disorders. However, targeting the root causes of these disorders will be a more effective approach. In disorders such as AD and MS, attempts are being made to treat the root causes discussed earlier. In HAD, the Highly Active Anti-Retroviral Therapy (HAART) has shown definite beneficial effects, but still better agents need to be developed. Although the anti-inflammatory agents could be neuroprotective, their roles are still limited. The novel therapies such as gene therapy are still at the stage of infancy. The bottom line is that the specific pharmacological treatment of the primary cause of most of the neuroinflammatory disorders is currently not available and general anti-inflammatory agents available on the market have limited scope. Development of suitable neuroprotective agents, therefore, needs urgent attention.

Therapy

Neuroprotective Agents

The synthesis of newer drug molecules employing principles of medicinal chemistry and drug designing is a rational approach for the development of novel drug molecules with neuroprotective abilities. However, natural sources should never be underestimated as they provide an important source for the development of new drugs. As an example, the ►Mediterranean diet largely consists of vegetables and fruits, and this could probably be the key to the healthy life of the aged population in that region. ►Ayurveda, the traditional Indian medicinal system still popular in India, is based on herbal medicines for the treatment of many disorders, including CNS disorders. Many modern medicines have their roots in nature.

Several naturally occurring molecules are being studied for their neuroprotective abilities. These could be divided into two groups, the first group targeting the root cause of the disease (specific in action), and the second group targeting the common pro-inflammatory mediators (Non-specific in action). The agents targeting the primary cause of the disease may also have direct actions against one or more of the pro-inflammatory mediators.

Group I Neuroprotective Agents of Natural Origin Targeting Primary Pro-Inflammatory Mediators

Attempts are being made to treat the primary causes of the brain disorders. The success rate is still low, and only a few agents are being targeted specifically to treat the root cause of the disease. Three of these agents with significant potential for the treatment of amyloidopathies and/or HIV associated neurological complications are discussed below.

The first example is curcumin**,** a polyhydroxy phenolic compound found abundantly in turmeric, the later being widely used in Indian curries as spice and in Ayurveda as a medicine. It has been shown to inhibit the formation of Aβ40 in an *in vitro* assay at an IC_{50} value at a concentration of 0.8 μM. It disaggregated Aβ40 at 1 μM concentration. The Aβ40 inhibition activity was more pronounced than that of ibuprofen and naproxen, the most commonly used NSAIDs for the treatment of inflammatory disorders. Unlike ibuprofen and naproxen, inhibition of Aβ formation by curcumin was dose dependent. The effect of curcumin on amyloid fibrils was dependent on fibril-related conformation, and not on Aβ sequence. Curcumin showed preferential staining of amyloid plaques in the brain, but weakly labeled NFTs. In an *in vivo* study, peripherally administered curcumin crossed the blood brain barrier (BBB), and reduced Aβ burden and plaque formation in transgenic mice. It suppressed Aβ formation in 17 month old transgenic mice (Tg2576). It also blocked Aβ mediated toxicity in SH-SY5Y neuroblastoma cells [7]. Based on this discussion, as well as the safety profile of curcumin demonstrated in other studies, it can be regarded as a potential candidate for the clinical trials.

Berberine is an isoquinoline alkaloid from *Coptidis rhizoama*. It was studied for its effect on APP production in APP_{NL}-H4 cells. It had neither cytotoxic effect on these cells, nor did it alter their morphology or

lactate dehydrogenase (LDH) release by these cells. Berberine did not show any change in the Aβ42/Aβ40 ratio, but reduced Aβ42 and Aβ40 levels in the cultured APP_{NL}-H4 cells. It did not alter APP expression levels or APP processing, but shifted the amyloidogenic processing of APP to a non-amyloidogenic pathway by increasing α-Secretase activity, and reducing β-Secretase activity [8]. Thus, berberine could possibly be used effectively for the treatment of AD or other amyloidopathies.

Propolis is a resinous substance collected by honey bees from plants. It protects against the entry of microorganisms and other creatures in the hive. It is a mixture of many compounds, relatively safe for human consumption, and is traditionally known for its medicinal properties. In a recent study, it was tested for its anti-viral properties in $CD4^+$ lymphocytes and microglial cells. When activated CD4+ lymphocytes infected with $HIV\text{-}1_{AT}$ and microglial cells infected with $HIV\text{-}1SF_{162}$ were treated with propolis, it inhibited the expression of HIV-1 in these cells in a dose dependent manner. Propolis from various geographic regions showed similar inhibitory activity. It was shown to inhibit the viral entry in $CD4^+$ lymphocytes, and also showed an additive effect on inhibition of HIV by AZT [9]. Thus, it offers significant potential in the treatment of toxic effects of HIV on brain microglial cells, and could possibly be safely combined with ►antiretrovirals (ARVs) for the treatment of HIV-associated complications.

Group II Neuroprotective Agents of Natural Origin Targeting Secondary Proinflammatory Mediators

As discussed earlier, neuroinflammation, immune activation and antioxidants play an important role in the etiology of AD, PD and HAD. Flavonoids that form an important part of the diet and other nutritional food supplements could be used in the prophylaxis and possible treatment of neuroinflammation associated with these disorders. A vast number of scientific data is available on the anti-inflammatory roles, neuroprotective abilities and therapeutic potential of flavonoids. They cover a broad range of compounds from simple polyphenolic compounds to phytoestrogens found in medicinal plants, fruits and vegetables. Naturally occurring polyphenols are active against free radicals, and are known to attenuate oxidative stress. Some of the flavonoids alter hormonal levels, whereas others show pharmacological manipulation of receptors in the brain and are able to modulate the neuronal activity. These compounds, with significant therapeutic potential to control damage due to pro-inflammatory mediators, are discussed in many reviews, and thus are not included in the current essay.

A strategy to evaluate the neuroefficacy and bioefficacy of dietary components and medicinal plants is described by Aruoma A, et al., 2003 [10]. Many flavonoids with anti-HIV abilities and reduction of gp120 from HIV infected C8166 (human T-lymphoblastoid) cells are also discussed in the aforementioned article. (−)Epicatechin-3-O-gallate, (−)Epicatechin, 3,3-,4-,5,7-penta-hydroxyflavan and Myricetin, 3,3-,4-,5,5-,7-hexahydroxy-flavone were found to be potent amongst them. As discussed in the aforementioned article, the reduced glutathione level found in many disorders of the brain including HIV associated brain disorders, PD and AD could be corrected by using flavonoids, which increase the glutathione level, and thereby increase the chances of survival.

There are also many complement regulatory molecules of herbal origin available for the treatment of inflammation. These are summarized, classified and their potential for the treatment of neuroinflammatory disorders discussed in a recent review by Kulkarni et al., [11]. Most of them have not been studied for their ability to offer ►neuroprotection, but theoretically may offer neuroprotection. Vaccinia virus complement regulatory protein (VCP) is a complement regulatory molecule of viral origin with neuroprotective potential and can serve as a role model for the development of complement based neurotherapeutics. Other potential complement regulatory molecules discussed in the aforementioned review [11] that can be used as neuroprotective agents are glycyrrhizin, rosmarinic acid, Kaemferol, polysaccharides, curacycline-A, apigenin and other flavonoids from olive oil. As discussed in the aforementioned review, the complement system is the final activation point of many pro-inflammatory mediators and complicates the brain environment by activating the immune cells to release other pro-inflammatory mediators. Thus, regulation of the complement system by using the complement regulatory molecules of herbal origin could be one of the rational approaches for the treatment and prevention of neuroinflammatory disorders.

Cautions While Using Herbal Medicines

While dealing with the herbal medicines, one should be aware of the potential side effects or drug interactions of these medicines. Interested readers should refer to a review article by W. Abebe [12], which mentions the interaction of ingredients of herbal origin with NSAIDs. As pointed out in this article, care should be taken while administering curcumin, ginseng or coumarin with NSAIDs. Aspirin is known to interact with ginkgo, garlic, ginger, bilberry, dong quai, feverfew, ginseng, turmeric, meadowsweet and willow which are known to have antiplatelet activity. Interaction of NSAIDs with these drugs may lead to internal bleeding. Acetaminophen may interact with gingko to increase the chances of bleeding. The analgesic effect of opioids may be decreased by ginseng. The

compounds of herbal origin form a part of many non-prescription medications. Thus, there is a need for thorough study, and knowledge of the adverse drug reactions, drug interactions and potential side effects of these drugs when combined with herbal treatments. While marketing herbal products, information regarding drug interaction and possible adverse reactions should be included in the label. In addition, proper optimization of the dose and bioavailability studies with a focus on appropriate route of administration is necessary for getting optimal benefit from these natural neuroprotective agents. All the ingredients to be used in neuroinflammatory disorders should either cross the blood brain barrier, or should be able to be delivered to the brain by alternative route of administration, such as via an intranasal route.

Conclusion

Neurodegenerative disorders are marked by the complexity of their pathogenesis. The primary etiologies of most of these disorders differ from each other, but most of them show some common pathological hallmarks. Ingredients of natural origin offer significant potential for the development of effective treatment strategies, by their specific actions on the root cause or by targeting common pro-inflammatory mediators. However, proper study of route of administration, bioavailability, side effects, adverse interactions and standardization of dose is necessary for the development of efficient neuroprotective agents.

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Central Nervous System Disease in Primary Sjögren's Syndrome

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Definitions

►Primary Sjögren's syndrome (pSS) is a chronic, multisystem autoimmune disorder characterized by dryness of eyes (keratokonjunctivitis sicca), mouth and other mucous membranes. Extraglandular manifestations are arthralgias, Raynaud's syndrome, pulmonary involvement, renal tubular acidosis, peripheral and central nervous system (CNS) disease. According to the revised international (American European Consensus Group) classification criteria [1], 4 out of 6 criteria (I. ocular symptoms, II. oral symptoms, III. objective ocular signs, IV. focal lymphocytic sialoadenitis, defined as at least one lymphocytic focus per 4 mm^2 of glandular tissue, i.e., a focus score ≥ 1 in a minor

salivary gland biopsy, V. objective evidence of salivary gland involvement obtained by the measurement of unstimulated salivary flow or by sialography and VI. presence of anti-SSA or anti-SSB antibodies) are required for the diagnosis of ►Sjögren's syndrome (SS), as long as either histopathological evidence (IV) or serologic evidence (VI) is present. Alternatively, three out of four objective criteria (III-VI) must be positive. The diagnosis of pSS implies the absence of an associated autoimmune rheumatic disease (secondary SS). The revised international classification criteria [1] were introduced as a standardized set of criteria intended to replace earlier classification systems [2,3].

CNS involvement in pSS includes cognitive impairment, psychiatric abnormalities and migraine as well as focal deficits resulting from meningoencephalitis, transverse myelitis and subarachnoid hemorrhage. The definition of CNS symptoms is limited to physical disability in some studies, but includes nonfocal symptoms such as subtle cognitive dysfunction in others [4].

Characteristics

Clinical Presentation

Primary Sjögren's syndrome is generally diagnosed between the ages of 30 and 60 years and affects women nine times as often as men. The main features are dry eyes and mouth, often involving caries, but the disease can become systemic and affect other organs, leading to symptoms such as muscle and joint pain, itchy skin, vaginal dryness, gastroesophageal reflux and dry cough. Among neurological findings, peripheral neuropathy is most common, affecting between 10 and 20% of patients. It may cause progressive and initially distal tingling/numbness and weakness of the upper and lower extremities (polyneuropathy), asymmetrical sensory and/or motor deficits (e.g., radiculopathy, multiple mononeuropathy) or cranial nerve dysfunction.

The symptoms and course of CNS involvement are also heterogeneous. Patients may experience a sudden onset of focal deficits, such as hemiparesis or speech disturbance, suggesting stroke. They may also develop symptoms subacutely (e.g., transverse myelitis, optic neuritis) or over months and years (e.g., chronic myelopathy), and the course of disease can be progressive or relapsing-remitting. Rarely, CNS disease in pSS may manifest as seizures. Symptoms are sometimes discrete and not easily detected in routine neurological exams. This applies especially to mild cognitive disturbances, which may reflect brain damage, but can also be associated with fatigue and/or depression, other common symptoms in pSS.

It is important to note that CNS disease may occur before typical sicca symptoms (►sicca syndrome) [5].

The prevalence of reported CNS disease is controversial and ranges from 0 to 62%. Reasons for the differences in prevalence in previous studies are (a) the use of diverging diagnostic criteria [1–3], (b) varying definitions of CNS involvement and (c) the selection of patients from varying populations [4]. To standardize the diagnostic criteria, the revised international (American European Consensus Group) classification criteria [1] were formulated in 2002. Definitions of CNS involvement differ regarding the inclusion or exclusion of nonfocal symptoms, specifically cognitive and neuropsychiatric disturbances. Studies disregarding patients with cognitive and neuropsychiatric impairment tend to underestimate the prevalence of pSS-related CNS symptoms. Moreover, a selection bias towards more severe CNS disease is likely to occur in tertiary referral centers, which may help explain the high prevalences reported in some hospital-based studies [6]. Another reason for discrepancies in the reported prevalence of CNS-involvement has recently been suggested: CNS disease may be more rarely associated with immunological markers of pSS than, for example, PNS involvement [5].

Pathology

Sjögren's syndrome is an autoimmune disorder in which immune cells destroy the exocrine glands that produce tears and saliva. At the beginning of the disease process, plasma cells and lymphocytes infiltrate the periductal salivary tissue. The original glandular structure is replaced by dense infiltrates of lymphocytes. Sjogren's syndrome may result from T-cell abnormalities or may be caused by a deficiency of T-lymphocytes and subsequent hyperactivity of B-lymphocytes and the production of autoantibodies. Both environmental and genetic factors are likely to contribute to the immunological dysregulation that occurs in pSS [7].

The mechanisms of neurological disease in pSS are still unclear. Regarding peripheral nervous system involvement, different mechanisms seem to be associated with specific clinical features. Thus, sensory ataxic, painful and trigeminal neuropathy may be related to more immediate neuropathic processes than multiple mononeuropathy and multiple cranial neuropathy, which appear to result from vasculitis [8].

Evidence on the pathology of CNS damage is diverse. Some studies have suggested ischemic mechanisms. Other possible mechanisms are mononuclear cell infiltration in CNS tissue, immunologically mediated CNS vascular damage and the action of antibodies (antineuronal and/or anti-Ro/SSA antibodies [5]). The types of tissue damage observed in pSS-associated CNS disease vary greatly, in accord with the heterogeneous mechanisms mentioned above. Thus patients may develop severe conditions resulting from vascular damage or obstruction, such as subarrachnoid hemorrhage and ischemia; other types of tissue injury, such as meningoencephalitis and transverse myelitis

indicate demyelination, and may be hard to distinguish from multiple sclerosis (MS).

Disease Markers

Immunological Markers

pSS is typically associated with anti-SSA/Ro and anti-SSB/La antibodies ►(Anti-SSA (Anti-Ro)/Anti-SSB (Anti-La) antibodies), of which anti-SSB/La is more specific to pSS, as well as with other anti-nuclear antibodies, antiphospholipid-antibodies, rheumatoid factor and cryoglobulins, which are elevated in numerous autoimmune diseases. Whether the presence of any of these immunological markers ►(disease markers) predicts the presence or severity of CNS involvement remains contradictory.

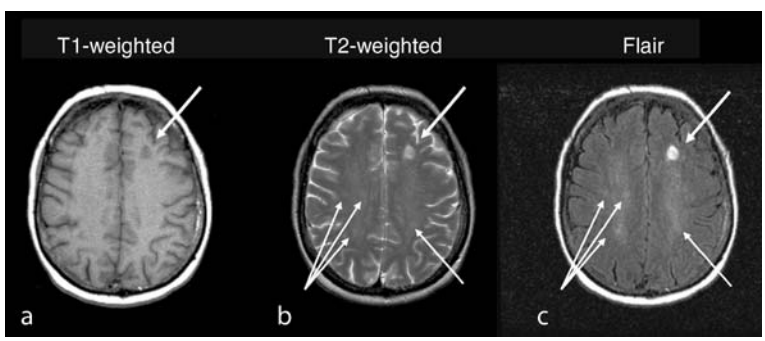
CNS-Imaging Markers

►CNS imaging, specifically ►magnetic resonance imaging (MRI), permits the detection of lesions as well as tissue atrophy in pSS. Large lesions, indicative of ischemia or hemorrhage have been identified. On T1-weighted MRI, which attributes tissue with high water content a low signal and tissue containing macromolecules (such as myelin) a relatively high signal, lesions involving severe damage of the tissue matrix appear hypointense. In contrast, T2-weighted MRI also reveals more subtle white matter damage, which occurs more commonly in pSS patients. FLAIR images, which are strongly T2-weighted and involve a nulling of cerebrospinal fluid, are especially sensitive to white matter lesions (Fig. 1). Because T2-weighted MRI is sensitive to increases in the concentration of free protons, it may indicate reversible edema as well as gliosis, demyelination and axonal loss. Conventional MRI is thus not sensitive to the type of white matter tissue damage. Furthermore, small white matter lesions are common in elderly individuals and are associated with cerebrovascular risk factors. Thus, it is not possible to use MRI as a simple marker of white matter damage in pSS, though recent studies have indicated an elevated number of white matter lesions in groups of pSS patients [4].

Brain atrophy has been reported in pSS patients, but not analyzed in a controlled study [4].

Previous MRI studies in pSS have largely been limited to conventional T2-weighted analyses of lesions. However, newer imaging techniques, which can provide more sensitive and/or specific information on tissue injury and have been successfully applied in other inflammatory CNS diseases, such as multiple sclerosis and systemic lupus erythematosus, are likely to become established in pSS research. ►Magnetization transfer imaging (MTI), for example, can help indicate the degree of tissue damage in selected regions as well as globally [9]. The principle underlying MTI is the selective saturation of protons bound to macromolecules such as myelin. In damaged tissue, the increased concentration of protons in free water leads to a quantifiable reduction of MT saturation effects. MT effects tend to be extensive in demyelinated tissue, less pronounced in vasculitic damage and discrete in edematous tissue. Moreover, MT effects can be detected in tissue that appears normal on conventional MRI. The high sensitivity of MTI makes it a potentially valuable marker of CNS tissue injury in pSS studies.

►MR-spectroscopy (magnetic resonance spectroscopy (MRS)) is another imaging technique likely to gain importance in the investigation of pSS-associated CNS pathology. By producing spectra that reflect levels of brain metabolites, MR spectroscopy conveys information on the type of potential tissue injury. For example, an elevated level of choline normalized to creatine (Cho/Cr) points to active demyelination or gliosis, whereas a decreased N-acetyl aspartate creatine (NAA/Cr) ratio is associated with neuronal dysfunction or loss [4]. This technique could, for example, help attribute



Central Nervous System Disease in Primary Sjögren's Syndrome. Figure 1 White matter damage in a patient with primary Sjögren's syndrome. T1-weighted MRI only indicates one relatively large lesion (a, *wide arrow*). T2-weighted MRI and FLAIR (b, c) are more sensitive to more subtle white matter abnormalities; on FLAIR images (c), the strong tissue contrast helps reveal small lesions more clearly than conventional T2-weighted MRI (b, *thin arrows*).

pSS-associated tissue damage to demyelination or to vasculitis.

In pSS patients with mild cognitive impairment or neuropsychiatric symptoms, functional imaging has revealed metabolic abnormalities in specific brain regions. ►Single photon emission computed tomography (SPECT), a nuclear medicine tomographic imaging technique based on gamma rays, has been used in pSS patients to assess regional brain metabolism. A tracer, such as ^{99m}Tc-HMPAO or ^{99m}Tc-ECD, is absorbed by brain tissue proportional to blood flow. By emitting gamma rays, the tracer permits the measurement of blood flow, which, in turn, is coupled to local brain metabolism. In pSS patients with neuropsychological disturbances, hypoperfusion has been identified in various brain regions including the frontal, temporal and parietal cortex as well as the striatum [4,10].

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Central Nervous System Infections: Humoral Immunity in Arboviral Infections

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Definition

This essay describes the humoral immune response during neurological infection caused by Arthropod-Borne Viruses.

Characteristics

Virus infections of the central nervous system (CNS) are relatively uncommon, but potentially devastating. The longevity of many cells in the CNS and the relative inaccessibility of this tissue to components of the immune system make the brain and spinal cord particularly susceptible to persistent virus infection. Clearance of virus from nonneural tissues often involves cytolytic elimination of the infected cells. Because of the potential for neurological damage by inflammatory mediators and cytotoxic cells, the brain has intrinsic mechanisms for controlling immune responses that are different from other organs. Nevertheless, immune responses to virus infection of the CNS can clear the virus from the tissue or sustain prolonged inhibition of virus replication without damage to the structure or function of the nervous system. The degree to which clearance is successful differs with the type of virus that causes the infection and with the target cells that the virus infects.

Of the ►viral infections of the CNS, ►meningoencephalitis and/or encephalomyelitis caused by ►arboviruses (Arthropod-Borne viruses) are among the most serious (►arboviral infection).

Arboviruses cause significant human illness ranging from mild, asymptomatic infection to fatal ►encephalitis or hemorrhagic fever. The most significant arboviruses causing human neurological illness

belong to genera in three viral families, Togaviridae, Flaviviridae, and Bunyaviridae. These viruses have a marked neurotropism, which leads to the characteristic pathological disease state. They may cause meningoencephalitis and/or encephalomyelitis often leading to a fatal outcome or permanent neurological sequelae such as neuropsychiatric symptoms in adults or mental retardation in children or paralysis of the extremities. The arboviruses most frequently involved in CNS infections in humans are listed in Table 1.

Here we report clinical symptoms and the humoral immune response in humans to the diseases caused by the principal virus transmitted by arthropods.

Description of the Process

Among animal viruses, arboviruses are unique in that they are transmitted by blood-sucking arthropods (vectors) to vertebrates, a mode of transmission commonly known as biological transmission involving the three essential components: virus, vector and vertebrate. Arboviruses generally require horizontal transmission by arthropod vectors among vertebrate hosts for their natural maintenance. On the basis of their arthopod vector, arboviruses that cause neurological infections can be classified as mosquito borne, tick borne, and viruses transmitted by different species of sandflies and by other vectors.

Togaviridae

Among mosquito-borne viruses some members of Alphavirus genus in the family Togaviridae represent an important group of neurological disease agents. Alphaviruses of neurological interest include Western Equine Encephalitis virus and Eastern Equine Encephalitis virus and Venezuelan equine encephalitis virus, which can cause severe disease in horses and encephalitis in humans. Human outbreaks of all three of these viral diseases occur shortly after outbreaks are observed in horses.

Alphavirus encephalitis results in either localized or diffuse signs of cerebral dysfunction. Signs of meningeal irritation (meningoencephalitis) are nearly always present but may not be evident in the very young, the very old or the comatose patients. Inflammation of the leptomeninges may occur in some patients without evidence of brain dysfunction (►aseptic meningitis). Onset of neurological disease is preceded by a period in which the patient has an influenza-like illness. Encephalitis may follow quite soon after the onset or may follow days or weeks later [1].

While in the New World the arboviruses of neurological importance belong to the Togaviridae family (with the exception of West Nile virus), in the Old World (Europe, Asia and Africa) the viruses involved belong to the Flaviviridae family and are transmitted by mosquitoes and by ticks, as illustrated in Table 1.

Flaviviridae

Flaviviruses that cause neurological disease can be classified on the basis of their mode of transmission as tick-borne or mosquito-borne viruses. In Europe the most important agent of human disease is the Tick-borne encephalitis virus (TBE), transmitted by ticks; in Southern and eastern Asia the Japanese encephalitis virus (JEV) is the most important pathogen transmitted by mosquitoes. Recently the Flavivirus West Nile spread from the Old World to America and since 1999 it represents an important cause of neurological disease in the United States.

Tick-Borne Viruses

Tick-Borne Encephalitis Virus (TBE)

The TBE virus species includes three sub-types, namely Far Eastern (previously RSSE), Siberian (previously west-Siberian) and Western European (previously Central European Encephalitis, CEE) virus.

The incubation period of the disease is usually 7–14 days, but it may vary from 2–28 days. The main clinical neurological syndromes associated with TBE are febrile headache, aseptic meningitis, meningoencephalitis, ►meningoencephalomyelitis, and post-encephalitic syndrome.

Encephalitis produced by European subtype viruses is biphasic with fever during the first phase and neurological disorders of differing severity, during the second phase, which occurs in 20–30% of patients. In contrast with severe Far Eastern subtype virus infections, those following infection by European strains are usually milder, mostly without sequels; case fatality rates are often as low as 1–2% and the disease in children is less severe than in adults.

Aseptic meningitis is the most common form of clinical TBE disease. It usually presents with high fever, headache, vomiting, and vertigo. Signs of meningeal irritation usually occur but may not be pronounced; however, all patients exhibit cerebrospinal fluid (CSF) pleocytosis.

Presentation of meningoencephalitis is variable. Meningeal signs are usually present, and patients are somnolent or unconscious. Severe tremors of extremities and fasciculations of the tongue, profuse sweating, asymmetrical paresis of cranial nerves, and nystagmus are common symptoms. In some patients, delirium and psychosis may develop rapidly (within hours).

Meningoencephalomyelitis is the most severe form of the disease. It is characterized by paresis that usually develops 5–10 days after the remission of fever. Severe pain in the arms, back, and legs occasionally precedes development of paresis. Involvement of cranial nerve nuclei and motor neurons of the spinal cord produces flaccid paralysis of the neck and upper-extremity muscles. Death may occur within 5–7 days of the onset of the neurological signs [2].

Central Nervous System Infections: Humoral Immunity in Arboviral Infections. Table 1 Major arboviruses that cause neurologic disease

Family (genus)/virus	Arthropod vector	Geographic distribution	Human disease	Occurrence
Togaviridae (Alphavirus)				
Eastern equine encephalitis	*Culiseta*, *Culex* mosquitoes and other species	North and South America	Febrile illness	Epidemic
			Encephalitis	
Venezuelan equine encephalitis	*Aedes*, *Culex* mosquitoes and other species	Central and South America, southern Florida	Febrile illness	Epidemic
			Encephalitis	
Western equine encephalitis	*Culex* mosquitoes	North and South America	Febrile illness	Epidemic
			Encephalitis	
Flaviviridae (Flavivirus)				
Japanese encephalitis	*Culex* mosquitoes	Asia, India, far-eastern former Soviet Union	Encephalitis	Epidemic
Murray Valley encephalitis	*Culex* mosquitoes	Australia, New Guinea	Encephalitis	Epidemic
Rocio	*Culex* mosquitoes	Brazil	Encephalitis	Epidemic
St. Louis encephalitis	*Culex* mosquitoes	North and South America	Encephalitis	Epidemic
West Nile	*Culex* mosquitoes and other species	Eurasia, Africa, North America	Encephalitis	Epidemic
			Encephalomyelitis	
Tick-borne encephalitis	*Ixodes*, *Dermacentor*, *Haemaphysalis* ticks	Europe, Russia, former Soviet Union	Encephalitis	Epidemic
				Endemic
Louping ill	*Ixodes ricinus* tick	Great Britain	Encephalitis	Rare - sporadic
Powassan	*Ixodes*, *Dermacentor*, *Haemaphysalis* ticks	Russia, North America	Encephalitis	Rare - sporadic
Bunyaviridae (Bunyavirus)				
California encephalitis	*Ochlerotatus* and *Aedes* mosquitoes	Western North America	Febrile illness	Rare - sporadic
			Encephalitis	
Jamestown Canyon	*Culiseta* and *Ochlerotatus* mosquitoes	North America	Febrile illness	Rare - sporadic
			Encephalitis	
La Crosse encephalitis	*Ochlerotatus* mosquitoes	North America	Febrile illness	Epidemic
			Encephalitis	
Snowshoe hare	*Ochlerotatus* and *Culiseta* mosquitoes	North America	Febrile illness	Rare – sporadic
			Encephalitis	
Bunyaviridae (Phlebovirus)				
Toscana	*Phlebotomus perniciosus, P. perfiliewi* sandflies	Europe, Mediterranean basin	Febrile illness	Epidemic
			Meningitis	Endemic
			Meningoencephalitis	
			Encephalitis	

Mosquito -Borne Viruses

Japanese Encephalitis Virus

The Japanese encephalitis virus (JEV) serocomplex includes other human pathogens such as West Nile virus, Murray Valley encephalitis, St. Louis encephalitis, and Kunjin viruses. JEV is a leading cause of childhood viral encephalitis in southern and eastern Asia and has also been a problem among military personnel and travelers to these regions.

Disease symptoms vary from a mild febrile illness to acute meningoencephalomyelitis. After an asymptomatic incubation period of 1–2 weeks, patients exhibit signs of fever, headache, stupor, and generalized motor seizures, especially in children. The virus invades and destroys the cortical neurons and causes encephalitis. This neuronal damage is similar to the destruction of anterior horn cells seen in poliomyelitis. The fatality rate ranges from 10–50% and most survivors have neurological and psychiatric sequels [3].

West Nile Virus

The West Nile virus (WNV) causes encephalitis in humans and horses. In humans, incubation ranges from 2–15 days. About 80% of WNV infections are asymptomatic, but some patients have symptoms ranging from mild febrile illness (>95% of patients) to meningitis or encephalitis (<1% of patients). People infected with WNV could experience fever, headache, and other non-specific symptoms that typically last for several days. Patients can also have a variety of other signs and symptoms including nausea, vomiting, macular-papular rash, chills, abdominal pain, muscle weakness, photophobia, conjunctivitis, movement disorders, parkinsonism, confusion, and slurred speech. For some patients, a febrile prodrome is immediately followed by encephalitis. More severe neurologic manifestations, such as a syndrome resembling poliomyelitis and acute flaccid paralysis, have been seen. The most severe complications are commonly seen in the elderly, with reported case fatality rates from 4–11% [3].

Bunyaviridae

The Bunyaviridae are a large group of viruses that infect a diversity of arthropod vectors and animal hosts. They have a worldwide distribution and can be the cause of human illness. The most important viruses in the family Bunyaviridae that produce neurological disease in humans belong to genus *Bunyavirus*, transmitted by mosquitoes and *Phlebovirus,* transmitted by different species of sandflies.

Genus Bunyavirus

The viruses that cause neurological disease are classified into the California serogroup: California encephalitis virus (CEV), La Crosse virus (LACV), Jamestown Canyon virus (JCV), and snowshoe hare virus. Symptoms range from unapparent or mild febrile disease to encephalitis and death. After a 3–7-day incubation period, sudden onset of fever, followed by stiff neck, lethargy, headache, nausea, and vomiting may be observed in infected individuals. Seizures have been seen in approximately half of the infected patients, and about 65% of the adult patients exhibit signs of meningitis. Seizures are the most important sequels in children and have been observed in approximately 10–15% of children 1–8 years after infection [4].

Genus Phlebovirus

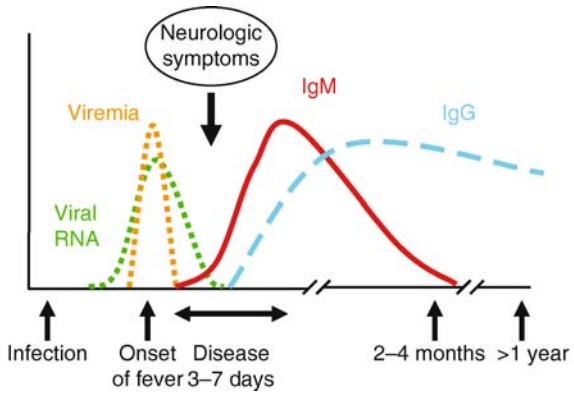
Viruses causing neurological disease are Toscana (TOS) virus and Rift Valley fever virus [5]. Although TOS virus infection in most cases consists of a mild disease with a favorable outcome, a small number of severe cases have been reported in the literature [6]. After an incubation period ranging from a few days to 2 weeks, disease onset is intense (70%) with headache (100%, 18 h – 5 days), fever (76%–97%), nausea and vomiting (67%–88%), and myalgias (18%). Physical examination may show neck rigidity (53%–95%), Kernig signs (87%), poor levels of consciousness (12%), tremors (2.6%), paresis (1.7%), and nystagmus (5.2%). In most cases reported so far, CSF contained >5–10 cells with normoglycorachia and normoproteinorachia. Blood samples may show leukocytosis (29%) or leukopenia (6%). The mean duration of the disease is 7 days, and the outcome is usually favorable.

Regulation of the Process

Alphaviruses

Studies on the structure and function of the various structural and non-structural proteins have been extensively conducted to understand the ►humoral immunity response to Alphaviruses infection.

Virus-specific IgM antibodies are detectable very early in human disease and often provides a means for rapid diagnosis of infection. Virus-specific immunoglobulin A (IgA) also appears early in infection, but declines rapidly. IgG antibodies appear in serum after 7–14 days and are maintained at relatively high levels for years. Rapidity of host antibodies synthesis is predictive of outcome from encephalitis because patients without evidence of antibodies at the time of illness are most likely to die. Accumulating data support the hypothesis that recovery from alphavirus infection is dependent primarily on the antibody response. Antibodies can neutralize virus infectivity and promote virus clearance by reticuloendothelial system (RES) in conjunction with complements. As described in Fig. 1 the infection is characterized by a biphasic course, viremia occurs during the febrile phase and ends when neurological symptoms appear. Appearance of antibodies correlates with cessation of viremia [7]. This specific characteristic is common to all neurological



Central Nervous System Infections: Humoral Immunity in Arboviral Infections. Figure 1 General course of symptoms of arboviral neurological diseases. The infection is characterized by a biphasic course. Viremia occurs during the febrile phase and ends when neurological symptoms appear. Appearance of antibodies correlates with cessation of viremia.

diseases caused by arboviruses, independently of their arthropod vector.

Flaviviruses

Susceptibility to flavivirus encephalitis implies a failure at some stage of the immune response that theoretically may be defined in either qualitative or quantitative terms. There is substantial clinical and experimental evidence for a correlation between protection against encephalitic disease and the presence of virus-specific antibodies, but the molecular and cellular basis for the development of this response has not been defined thoroughly. In studies that have shown protection by antibodies, the roles of other immune system components in the process have not often been assessed. Furthermore, there is increasing evidence that flaviviruses have evolved mechanisms to manipulate the effector functions of both innate and adaptive immune responses. The magnitude and importance of these responses probably vary from one experimental model to another and account for differences observed in studies that have examined the immune system in the context of a either a primary or a memory response [8].

Extensive studies have been conducted in JEV patients. In humans infected with JEV a rapid and potent antibody response has been observed. Serum IgM to the virus can be detected in many patients when symptoms first appear, by the seventh day of disease, and can be detected in most survivors. On the other hand, there are patients who succumb so rapidly to Japanese encephalitis that antibody levels remain undetectable at death (diagnoses being made by isolation of the virus from brain). Antibodies are directed in part against the envelope (E) glycoprotein and therefore have virus-neutralizing (►neutralizing antibody) and ►hemagglutination-inhibiting activity, and in part against virus non-structural proteins NS1, NS3 and NS5.

Antibody synthesis undergoes class switching so that IgGs to JEV can be detected in most patients within 30 days of disease onset. In patients previously infected with another flavivirus (e.g. dengue virus), there is an anamnestic response to flavivirus-group common antigens so that IgGs to JEV are present sooner and in greater quantities.

Antibody levels are lower in instances of subclinical infection compared to disease. A correlate of that phenomenon is the longer persistence of IgM to JEV observed in clinically severe versus mild infections; serum IgM to the virus can be measured in some patients 1–2 years after convalescence. Thus, in some patients, antibody responses reflect the severity of disease, possibly correlating with the duration and extent of virus replication.

Anti-viral IgM and IgG are present in CSF of patients with overt Japanese encephalitis but not in those infected subclinically. B cells and differentiated plasma cells are present in the perivascular cuffs of brain tissue from fatal encephalitis, as well as in CSF during acute disease. CSF leukocytes collected during acute Japanese encephalitis spontaneously produce IgM and IgG to JEV; moreover, antibody levels in CSF are greater than those in serum. These data provide a pathophysiologic basis for regarding CSF IgM to JEV as a marker of virus localization within the CNS [9].

While Flavivirus diseases have been extensively studied, only few information are available for neurological diseases caused by Phleboviruses.

Phleboviruses

The principal studies have been conducted on Toscana virus that has been considered as one of the emerging disease in Europe.

In Toscana virus patients, IgM antibodies, usually present at the onset of symptoms, can reveal elevated titers by enzyme-linked immunosorbent assay (ELISA). IgM antibodies are detected in serum of patients 4–5 days after the onset of symptoms, reaching their highest titer 1–4 weeks after, and can persist for at least 1 year. IgG antibodies can be absent at the onset of symptoms: titers rise in convalescent sera and persist for many years. High titers of neutralizing antibodies are present in convalescent sera (range from 1:40–1:2,560). However, there appeared to be no correlation between the severity of illness and the subsequent titer of neutralizing antibodies.

At least five proteins have been identified in Toscana virus-infected cells: nucleoprotein N, glycoproteins G1 and G2, a large protein (L) assumed to be a component of the polymerase, and two nonstructural proteins, NSm and NSs. Immunoblotting and semiquantitative radioimmunoprecipitation assay (RIPA) allow

identification of nucleoprotein N as the major antigen responsible for both IgM and IgG responses. Antibodies to glycoproteins are detected in about one-third of patients, and their presence always predicts neutralizing activity. Antibodies to non-structural proteins NSm and NSs are also identified. These results raise some questions about antigenic variability and relevant ►neutralization epitopes of Toscana virus [10].

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Central Nervous System Inflammation: Astroglia and Ethanol

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Synonyms

Alcohol; Astrocytes: Neuroinflammation

Definition

Long-term chronic and acute, binge-type alcohol (ethanol) consumption disrupts cognitive function and causes structural brain damage. The adverse effects of ethanol are typically realized when blood ethanol levels reach 20–50 mM; however, blood ethanol concentrations have been reported to exceed 200 mM. Among the cells profoundly affected by ethanol are the astroglia. Astroglia are the most prevalent cell type in the human central nervous system (CNS) and perform important roles both in normal tissue homeostasis and response to injury and infection. Physiological functions of astroglia include neurotrophic factor production, regulation of neuronal development and function, neurotransmitter metabolism and extracellular regulation of pH and K^+concentration and they comprise a critical component of the ►blood-brain barrier (BBB). Important astroglial derived inflammatory mediators include cytokines, ►chemokines, inducible nitric-oxide synthase (iNOS), and cyclooxygenase type-2 (COX-2). These inflammatory molecules are involved in the highly orchestrated sequence of events whereby peripheral immune cells and resident glia are activated and recruited to the affected brain region. Activated immune cells and glia are instrumental in the clearance of infectious and foreign agents, promotion of neuronal survival and tissue repair. With prolonged inflammation, these protective and repair activities are lost and neurotoxicity ensues. Increasing evidence suggests that ethanol-induced brain damage may be, in part, related to modulation of neuroinflammation. Similarly, excessive ethanol intake appears to compromise CNS immunocompetence.

Characteristics

Description of the Process

It is well known that alcohol abuse results in structural and functional damage to the brain. Damage to the CNS is clearly evidenced in alcoholic individuals by a significant reduction in both brain weight and brain volume compared to control subjects. Interestingly, the neuropathology caused by alcohol appears to be region and cell type specific. For instance, the cerebral cortex, hypothalamus and cerebellum are quite vulnerable to the adverse effects of alcohol. Additionally, while both neurons and astroglia are affected by alcohol, astroglia are particularly susceptible to the detrimental effects of alcohol. Ethanol alters astroglial cell function and proliferation and the reduction in brain size is likely due in part to the cytotoxic effects of ethanol on astroglia. These ethanol-mediated effects on astroglia are potentially very important given that astroglia are essential for neuronal survival and function and are instrumental in response to infectious and traumatic insults to the CNS. The mechanism responsible for ethanol-induced brain damage is not fully understood but a major contributor appears to be inflammation. That is, ethanol

induces inflammation in the brain and alters inflammatory pathways in the brain. These changes in inflammatory pathways likely contribute to brain damage but may also alter CNS immunocompetence and response to injury. For instance, risk and fatality of bacterial meningitis is greater in patients with alcoholic liver cirrhosis than in patients with non-alcoholic cirrhosis [1]. The poor outcome of alcoholic individuals with bacterial meningitis is likely a consequence of altered BBB function and CNS immunocompetence, given the involvement of BBB breakdown, leukocyte infiltration and neuronal injury in the pathogenesis of bacterial meningitis. Another instance in which alcohol abuse may be particularly detrimental to infection related neuropathogenesis is ►human immunodeficiency virus (HIV) infection. More specifically, neuroimaging analysis indicates common loci of neuropathology in the human brain between HIV infected and alcoholic individuals suggesting that co-occurrence of these diseases may compound neuropathology [2]. Experimental findings suggest that ethanol and the HIV protein, ►Tat protein, synergistically increase oxidative stress and proinflammatory gene expression in the brain [3]. These clinical insights, as well as other key experimental findings have led researchers in the field to target several inflammatory molecules as likely molecules involved in ethanol modulation of CNS immunocompetence and response to injury. The remainder of this essay will discuss key insights regarding ethanol effects on these inflammatory molecules.

Regulation of the Process

Nuclear Factor (NF)-κB

The transcription factor, ►nuclear factor kappa B (NF-κB) plays a pivotal role in inflammatory and immune related responses in astroglia. *In vitro* studies indicate that ethanol effects on NF-κB activation in astroglia vary, depending on the origin of the astroglial cells (i.e., species or among different cell lines within a species), and the stimulus used to activate NF-κB. In human astroglial cells, ethanol enhances cytokine-induced NF-κB activity as indicated by increases in nuclear levels of the RelA (p65) subunit of NF-κB. Furthermore, in A172 astroglia, ethanol enhances cytokine stimulated NF-κB-DNA binding [4]. However, it is unclear whether this ethanol-mediated increase in p65 protein is a consequence of enhanced entry into the nucleus or reduced degradation or export. Seemingly in contrast, in a separate human astroglial cell line, ethanol inhibits carbachol-stimulated NF-κB activity [5]. Together these findings suggest that the mechanism by which ethanol modulates NF-κB activation differs with activation pathway and cell type. It is also important to note that other NF-κB proteins (i.e., p50, p52, c-Rel and Rel-B), as well as associated regulatory proteins such as inhibitor of NF-κB (IκB) and IκB kinase (IKK) may also be affected in astroglia by ethanol. Further investigation is necessary to identify the specific molecular sites of ethanol action.

Inducible Nitric-Oxide Synthase

The inducible isoform of nitric-oxide synthase (iNOS) is not usually present in the healthy CNS. However, following traumatic or pathologic insult, iNOS is transcriptionally induced via an NF-κB-dependent mechanism, particularly in the affected astroglia. iNOS subsequently catalyzes the generation of nitric oxide (NO) in the region of the activated astroglia. Induction of astroglial iNOS, which is instrumental in response to injury and immunocompetence within the CNS, is modulated by ethanol exposure [6]. For instance, proinflammatory-induced iNOS expression in rat astroglial cells is inhibited by ethanol. In contrast, cytokine-induced iNOS expression in human astroglial cells is biphasically modulated by ethanol such that lower concentrations enhance iNOS expression and higher levels are inhibitory. In some astroglial cell models, ethanol exposure alone is sufficient to induce iNOS expression [6]. Hence, ethanol effects on astroglial iNOS expression are stimulus and cell-type dependent. The mechanism by which ethanol modulates iNOS expression in astroglia is not completely understood. Increasing evidence suggests that ethanol modulates inflammatory-induced iNOS expression by altering the transcription of iNOS. Given the integral role of NF-κB in iNOS activation and sensitivity of this transcription factor to ethanol it may be speculated that ethanol disrupts iNOS expression in part via an NF-κB-dependent mechanism [4].

Cyclooxygenase-2

The inducible isoform of cyclooxygenase, ►cyclooxygenase-2 (COX-2) is instrumental in the production of prostaglandin E_2 (PGE_2) from arachidonic acid. Increased expression of COX-2 and prostaglandin production following traumatic or pathologic insult in the CNS is involved in inflammatory-mediated neuropathogenesis. Enhanced expression and activity of COX-2 in astroglia may be involved in ethanol-induced brain damage given that ethanol-induced overexpression of COX-2 occurs predominantly in astroglia not neurons. Similar to what has been observed for astroglial iNOS, ethanol up-regulates astroglial COX-2 through an NF-κB-dependent mechanism. Furthermore, ethanol-induced neurotoxicity can be blocked through inhibition of NF-κB or specific inhibition of COX-2 [7]. The mechanism by which ethanol alters NF-κB signaling to attenuate COX-2 activation remains to be elucidated.

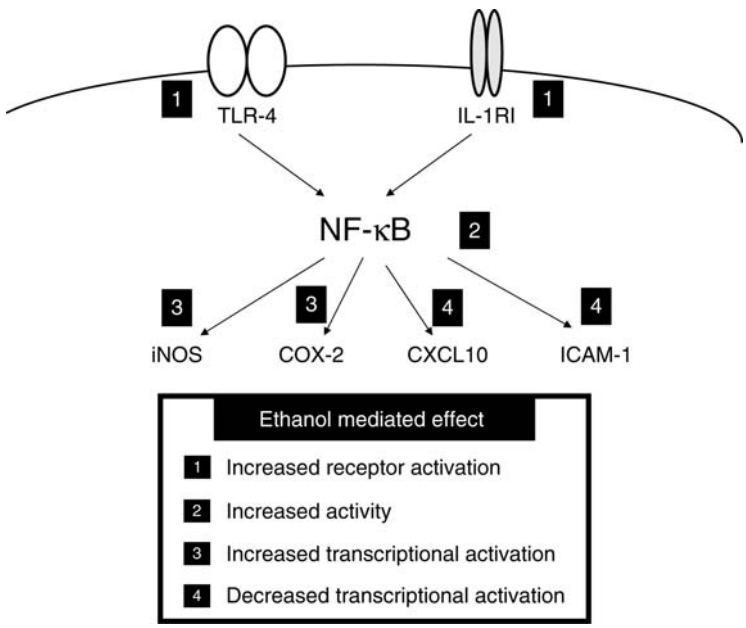
Toll-Like Receptor-4 and Type I Interleukin-1 Receptors

Bacterial lipopolysaccharide (LPS; endotoxin) and interleukin-1β (IL-1β) stimulate astroglial expression of inflammatory mediators through activation of the ►Toll-like receptor (TLR)-4 and IL-1RI receptors,

respectively. Ethanol-induced inflammation is attenuated when TLR-4 and IL-1RI activation is blocked [8]. More specifically, antagonism of these receptors prevents ethanol induced activation of NF-κB and subsequent induction of iNOS and COX-2. The activity and function of TLRs other than TLR-4 may also be modulated by ethanol. It is yet unclear, however, whether ethanol directly or indirectly alters the activation or function of these receptors. Additionally, TLR's other than TLR-4 may also be ethanol-sensitive and therefore, may be important in ethanol effects on inflammatory signaling in astroglia.

Intercellular Adhesion Molecule-1

The glycoprotein, intercellular adhesion molecule (ICAM)-1 is constitutively expressed on the surface of multiple cell types including astroglia. As a ligand for integrin receptors on leukocyte cell surface membranes, this molecule is instrumental in leukocyte migration. While the importance of ICAM-1 on astroglia has not been fully elucidated, this adhesion molecule seems to be instrumental in neuroinflammation. Involvement of ICAM-1 in neuroinflammation is evidenced by increased expression of ICAM-1 on astroglia following exposure to inflammatory stimuli. Also, recruitment of leukocytes into the CNS involves ICAM-1 and activation of astroglial ICAM-1 results in the expression of an array of inflammatory cytokines. These astroglial events are likely involved in sustaining the inflammatory response within the CNS. The enhanced cell surface expression of ICAM-1 on astroglia following proinflammatory stimulation is prevented by ethanol exposure [9]. The ethanol mediated reduction in ICAM-1 protein expression results in part from reduced ICAM-1 mRNA expression [9]. In addition to the effects of ethanol on ICAM-1 transcription, ethanol may also modulate posttranscriptional or posttranslational events that influence cell surface expression; however, the mechanistic



Central Nervous System Inflammation: Astroglia and Ethanol. Figure 1 Schematic representation of the ethanol-sensitive sites which may influence inflammatory signaling in astrocytes. The exact mechanism by which ethanol modulates inflammatory signaling in astrocytes remains unclear. However, as gleaned from several in vitro models of neuroinflammation, there are multiple ethanol-sensitive sites in astrocytes that may impact CNS immunocompetence and response to brain injury in alcohol abuse. Ethanol alters signaling through two cell surface receptors, toll-like receptor (TLR)-4 and type 1 interleukin (IL)-1 receptors, which are activated by bacterial lipopolysaccharide (LPS) and IL-1β, respectively. Following activation of the receptors, signal transduction cascades are activated, many of which activate the transcription factor nuclear factor (NF)-κB, which is central to inflammatory signaling in astrocytes and consistently implicated in ethanol mediated effects on neuroinflammation. NF-κB transactivation is instrumental in the induction of numerous genes which encode for inflammatory proteins including inducible nitric-oxide synthase (iNOS), cyclooxygenase type 2, chemokines (i.e., interferon-γ inducible protein or CXCL10) and intracellular adhesion molecule-1. Additional studies are warranted in order to identify the molecular mechanisms through which ethanol alters the expression and/or activity of these inflammatory molecules. Subsequent studies are also needed to determine the interactive effects of ethanol on multiple target molecules in a given astrocyte or astrocyte population.

details remain to be elucidated. Similarly, the consequences of ethanol-induced changes in astroglial ICAM-1 expression are uncertain.

CXC Chemokine Ligand 10

Important functions of chemokines within the CNS include recruitment, activation and proliferation of leukocytes, microglia, and astrocytes. One chemokine that has emerged as instrumental in both physiological and pathological events in the CNS is interferon-γ inducible protein or CXCL10. Indeed, infection within the CNS and injury to the brain is often associated with enhanced astroglial CXCL10 expression in the affected region. Thus, it appears that astroglial CXCL10 has an integral role in CNS immunocompetence and response to injury. Ethanol-induced changes in astroglial CXCL10 expression could potentially compromise CNS immunocompetence or be involved in ethanol-induced CNS pathologies. In fact, ethanol has been found to modulate CXCL10 expression *in vitro* and *in vivo*. It has been demonstrated *in vitro* that LPS + IL-1β stimulates CXCL10 production in human astroglial cells [10]. However, chronic exposure to ethanol attenuates proinflammatory induced CXCL10 expression in astroglia [10]. The functional importance of ethanol effects on astrocytes has been demonstrated using astroglial-mediated leukocyte chemotaxis. That is, exposure of astroglial cells to LPS + IL-1β increases release of chemotactic factors that induce leukocyte chemotaxis. Involvement of CXCL10 in this model of astrocyte-mediated leukocyte chemotaxis is evidenced by the fact that anti-CXCL10 neutralizing antibody reduces astroglial-mediated leukocyte chemotaxis. Importantly, chronic exposure of astroglia to ethanol inhibits astroglial-mediated leukocyte chemotaxis, presumably in part, through a reduction in astroglial CXCL10 production. The mechanism by which ethanol modulates chemokine production in astroglia is still unclear. Ethanol likely alters CXCL10 expression by altering transcription of CXCL10 mRNA, but it is also possible that ethanol modulates specific upstream signal transduction events that are instrumental in chemokine expression [10].

There is much work to be done in order to fully appreciate the cellular and molecular mechanisms by which ethanol alters inflammatory pathways in astroglia. Furthermore, the differential effects of acute and chronic ethanol exposure on astroglial inflammatory pathways also need to be determined. While several ethanol-sensitive targets likely exist, NF-κB is central to neuroinflammation and consistently implicated in the ethanol-mediated effects on astroglial inflammatory mediators (Fig. 1). Further analysis of this transcription factor and its numerous associated proteins may provide important insights into the mechanism by which ethanol alters neuroinflammation. These insights may foster novel therapeutic strategies to treat and prevent alcohol-mediated neuropathogenesis.

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Central Nervous System Inflammation: Cytokines and JAK/STAT/SOCS Signal Transduction

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Definition

►Cytokines are key effectors of cellular communication in many pathophysiological states that affect the

central nervous system (CNS). Cytokine communication depends upon a molecular circuitry consisting of cell surface receptors and multiple receptor-coupled intracellular signaling pathways that determine the timing, nature and strength of the cellular response to an external cytokine stimulus. Pivotal in the action of a great many cytokines are the receptor-associated Janus tyrosine kinases (JAKs) and their substrates, latent cytoplasmic transcription factors termed signal transducers and activators of transcription (STATs) (for review see: [1]). The duration and intensity of cytokine-activated JAK/STAT signaling is subject to control by physiological feedback inhibitory proteins known as the suppressors of cytokine signaling (SOCS).

Characteristics

Quantitative Description

There are four members of the JAK family (JAK1, JAK2, JAK3 and TYK2) and seven members of the STAT family (STAT 1, 2, 3, 4, 5A, 5B and 6). JAKs have a molecular weight of 120–140 kDa and contain seven JAK homology (JH) domains. The C-terminal JH1 domain has tyrosine kinase activity while JH2 has a pseudokinase structure but no catalytic function and regulates JAK activity. Regions JH3 to JH7 are required for interaction with the receptor. The molecular weight of the seven STATs ranges from 80 to 115 kDa. They also show a related structure with an N-terminal dimerisation domain and a central SH2-domain that are required for STAT dimerisation. The SH2 domain also contains a conserved tyrosine residue that serves as a substrate for the JAKs. Phosphorylation of this tyrosine is essential for STAT activity. Adjacent to the dimerisation domain are a coiled-coil domain that is involved in protein-protein interactions and the DNA binding domain. The transcriptional activation domain (TAD) is close to the C-terminus.

The SOCS family currently contains eight members, SOCS1-SOCS7 and CIS that range in molecular weight from 22 to 63 kDa. Members of this family share two common motifs – a central SH2 domain interacts with phosphorylated tyrosine residues and the C-terminal SOCS-box mediates ubiquitination and degradation of the SOCS protein.

Description of the Process

JAK and STAT Activation

Many cytokines and hormones that use type I or type II cytokine receptors mediate their biological effects via JAK/STAT signaling pathways including the colony stimulating factors, ►interferons, many interleukins (e.g., IL-2, 3, 4, 5, ►interleukin 6, 10 and ►interleukin 12), leukemia inhibitory factor (LIF), ciliary neurotrophic factor, growth hormone, prolactin, erythropoietin and leptin (Fig. 1) [1]. Binding of a cytokine to its cognate receptor triggers tyrosine phosphorylation and activation of specific JAKs (Fig. 2). These kinases phosphorylate tyrosine residues on multiple target proteins, including each other as well as cytoplasmic domains of the receptor. The receptor chain phosphotyrosine sites then interact with SH2 domains on STAT molecules. After recruitment to the receptor, STATs also become phosphorylated on specific tyrosine residues by the JAKs, before dissociating from the receptor. These activated STAT monomers form dimers that translocate to the nucleus and bind to specific DNA target sequences located in the promoter regions of genes thereby modulating transcriptional activity. Importantly, individual cytokines activate specific STATs thus conferring the specificity of the cellular response. For example, IL-6 signals via activated STAT3 homodimers while IFN-γ uses activated STAT1 homodimers.

Abbreviations: CIS, cytokine-inducible SH2 protein; CNTF, ciliary neurotrophic factor; CSF, colony stimulating factor; CT, cardiotrophin; Epo, erythropoietin; G-CSF, granulocyte colony stimulating factor: GM-CSF, granulocyte macrophage colony stimulating factor; GPCR, G-protein coupled receptor; IFN, interferon; IL, interleukin; JAK, Janus kinase; MCP-1, monocyte chemotactic protein-1; MIP-1α, macrophage inflammatory protein-1 alpha; RANTES, regulated on activation, normal T-cell expressed and secreted; SDF1-α, stromal derived factor 1 alpha; STAT, signal transducer and activator of transcription; SOCS, suppressors of cytokine signaling; Tyk2, tyrosine kinase 2.

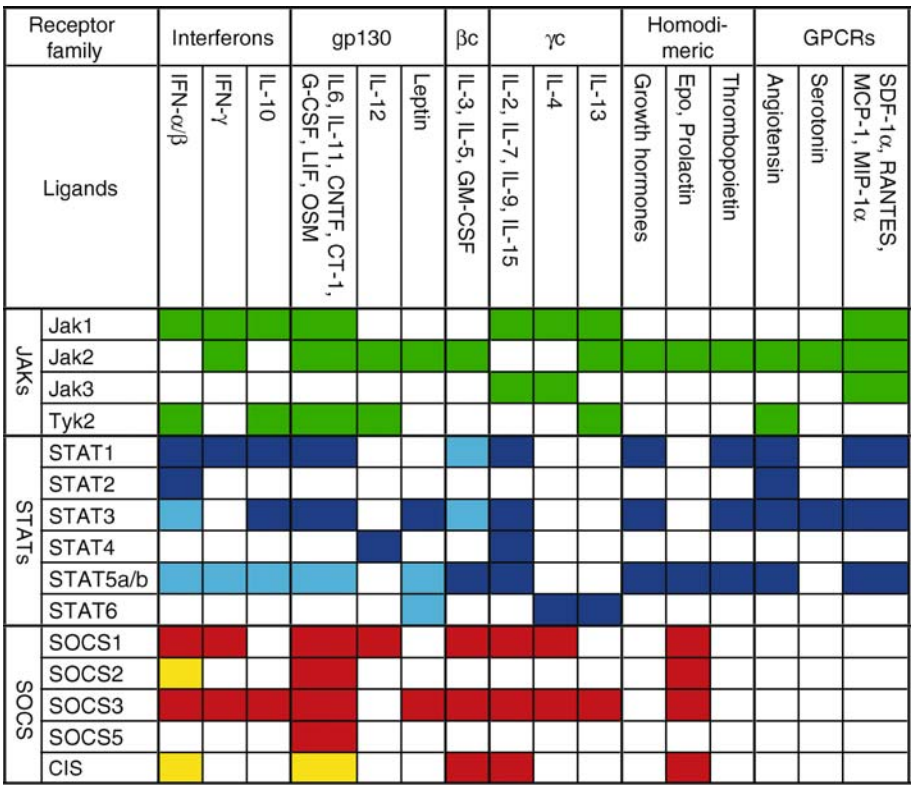
Regulation of JAK/STAT Signaling Through SOCS

Mechanisms exist to downregulate the JAK/STAT signaling cascade and thereby avert potentially damaging consequences of unrestrained cytokine signaling. SOCS constitute an important physiological feedback mechanism for self-limiting the cellular cytokine response. There are multiple targets through which the SOCS molecules inhibit cytokine-activated JAK/STAT signaling (Fig. 2). For example, SOCS1 can directly associate with high affinity, with all four JAK molecules, directly inhibiting their catalytic activity while SOCS3 functions in part, by interacting with activated cytokine receptors resulting either in the inhibition of JAK activity or blocking STAT binding.

Regulation of the Process

STATs and SOCS in Neuroinflammatory Disorders

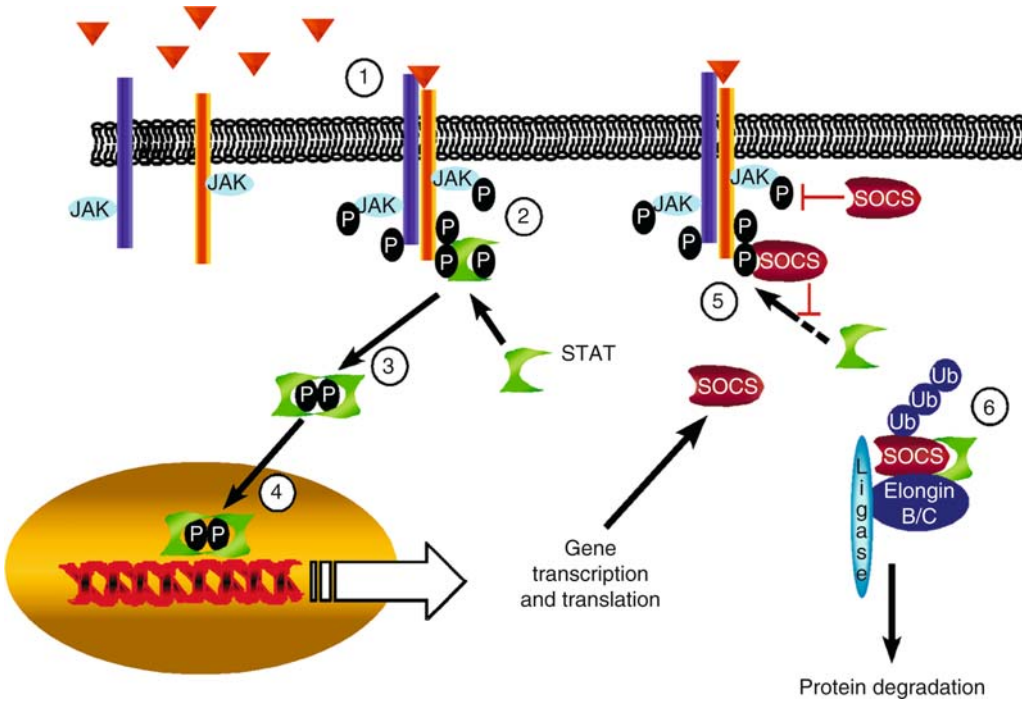
Our current understanding of cytokine signaling and its regulation in the CNS during neuroimmune diseases comes mostly from studies in animal models [2,3]. ►Experimental autoimmune encephalomyelitis (EAE) is an animal model for the human disease multiple sclerosis (MS). In EAE, autoreactive T- and B-cells infiltrate the CNS leading to demyelination, loss of oligodendrocytes and some axonal injury. Prominent cytokine production occurs in the CNS of mice with



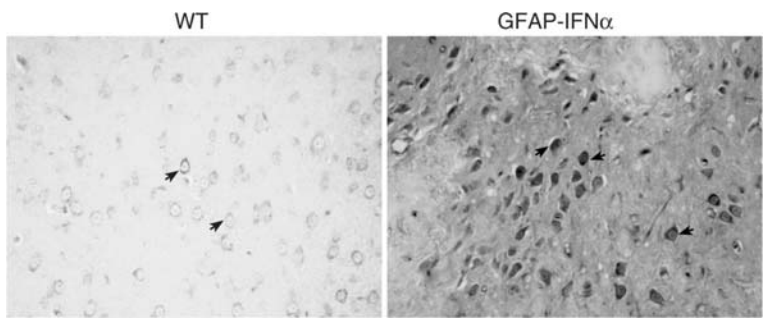
Central Nervous System Inflammation: Cytokines and JAK/STAT/SOCS Signal Transduction.
Figure 1 Utilization of JAKs, STATs and SOCS for signal transduction by some selected cytokines, hormones and growth factors. The JAK/STAT signal transduction pathway is central to the action of the majority of cytokines. On the whole the specific biological responses of cells to individual cytokines is the culmination of the activation of different STAT molecules. Here, ligands are grouped and combined according to receptor family. Reported activation of a specific JAK (*green*), STAT (*dark blue*) or SOCS (*orange*). In addition, light blue indicates reported alternative activation of STATs. Note, unstained cells do not necessarily mean absence of activation but rather no scientific reports are known to the authors.

EAE and includes elevated levels of IFN-γ, IL-1, IL-6 and TNF. In addition, ►transgenic mice developed by us with CNS-restricted, astrocyte production of the key host defense cytokines IL-12 or IFN-α develop a cell-mediated immune response with T-cell activation and the production of IFN-γ causing demyelination and neurodegeneration or inflammatory encephalopathy with neurodegeneration. Analysis of these different neuroinflammation models revealed stimulus- and cell-specific upregulation of various STAT and SOCS mRNAs and or proteins. In all three neuroimmune models, elevated STAT1 protein is found in a number of neural cells including neurons, microglia, astrocytes and oligodendrocytes where it exhibits nuclear localization consistent with activation (Fig. 3). Both IFN-α and IFN-γ activate STAT1 as a key mechanism in the ►signal transduction process mediated by these cytokines. The levels of STAT3 and STAT4 proteins also increase in the CNS of mice with EAE and transgene-encoded IL-12 while STAT3 is activated in the CNS of mice with transgene encoded IFN-α [4]. However, in contrast with STAT1, the localization of the STAT4 and STAT3 proteins is restricted to infiltrating T-lymphocytes (STAT4) and macrophage/microglia (STAT4 and STAT3). Since IL-12 is known to signal predominantly through STAT4 it is clear that T-cells and possibly other immune cells (e.g., NK cells), recruited to the CNS are the principal cellular targets of locally produced IL-12 and respond with increased production of IFN-γ. The absence of STAT4 in resident CNS cells indicates that these cells are non-responsive to IL-12 but, conversely, via STAT1 are highly responsive to the IFNs, IFN-α and IFN-γ. Interestingly, and similar to STAT4, SOCS1 and SOCS3 RNA are also increased in the CNS of the IL-12 transgenic mice and mice with EAE, and are found largely in infiltrating mononuclear cells.

In summary we can say that cells intrinsic to the CNS such as neurons and oligodendrocytes respond vigorously to cytokines such as IFNs with strong positive feed forward regulation of the JAK/STAT signal transduction pathway leading to significant increases in



Central Nervous System Inflammation: Cytokines and JAK/STAT/SOCS Signal Transduction.
Figure 2 A generic JAK/STAT signaling pathway and its feedback inhibition by SOCS. (i) Binding of a cytokine to its receptor causes receptor subunit association. (ii) Receptor-associated JAKs are brought into close proximity resulting in JAK tyrosine phosphorylation/activation and JAK-mediated receptor chain tyrosine phosphorylation followed by STAT recruitment and JAK-mediated tyrosine phosphorylation of the STAT. (iii) Phosphorylated STAT molecules dissociate from the receptor chain and form dimers. (iv) Nuclear translocation of STAT-dimer and binding to specific DNA recognition sites modulates the transcriptional activity of target genes such as SOCS genes that are induced. (v) SOCS bind to JAKs thus inhibiting their catalytic activity or prevent STAT-binding to the receptor. (vi) SOCS-mediated complex formation with elongin B and C and a putative E3 ubiquitin ligase involved in the proteosomal degradation of the SOCS molecule and the bound STAT.



Central Nervous System Inflammation: Cytokines and JAK/STAT/SOCS Signal Transduction. Figure 3 STAT1 is elevated in the brain of mice with chronic production of IFN-α. Sections of brain from a wild type (WT) or a transgenic mouse (termed GFAP-IFNα) with astrocyte-targeted production of the type I IFN, IFN-α. Sections were stained by immunohistochemistry using a polyclonal antibody against murine STAT1. The STAT1 molecule forms part of the canonical IFNAR-coupled JAK-STAT signal transduction pathway that mediates the actions of type I IFNs such as IFN-α. Neurons in healthy WT mice show only low expression of STAT1 protein that is located predominantly in the cytoplasm (*arrows*). By contrast, levels of STAT1 are much higher in neurons of GFAP-IFNα mice and STAT1 is also found in the nucleus (*arrows*). This is indicative of activation of STAT1 and coincides with STAT1-dependent gene transcription.

these cells in the expression of a number of target genes. However, under these conditions *in vivo*, these cells also exhibit a relative deficiency in SOCS1 and SOCS3 which may compromise their ability to negatively regulate JAK/STAT signaling activated by these cytokines. As discussed in more detail below, one consequence of this may be to predispose these cells to cytokine-mediated injury during immunoinflammatory states.

Consequences of Dysregulated JAK/STAT/SOCS Signaling in Cytokine-Mediated CNS Responses

As we have seen the cerebral expression of various STATs, their activation, as well as that of the major physiological inhibitors of this pathway, SOCS1 and SOCS3, is highly regulated in a stimulus- and cell-specific fashion. Recent work has begun to focus on the relationship between the JAK/STAT/SOCS activity and biological responses to cytokines in the CNS.

Deficiency of STAT1 or STAT2 Alters IFN-α Induced Disease in the CNS

Transgenic mice (termed GIFN) with astrocyte-targeted production of IFN-α while resistant to CNS viral infection, develop progressive neurodegenerative disease with inflammation and calcification associated with increased expression of IFN-regulated genes and activation of the IFN-signaling molecules STAT1 and STAT2. The role of STAT1 or STAT2 in mediating the actions of IFN-α has been explored by generating GIFN mice null for these STAT genes [5,6]. Surprisingly, and despite the loss of signaling activity and downstream target gene modulation associated with these STAT molecules, these animals develop either more severe and accelerated neurodegeneration with calcification and inflammation (GIFN/STAT1 null) or severe inflammation and medulloblastoma (GIFN/STAT2 null). In GIFN/STAT2 null mice the formation of medulloblastoma was linked to chronic autocrine stimulation of granule neuron proliferation caused by IFN-γ stimulated STAT1-dependent activation of the sonic hedgehog (Shh) signaling pathway. Shh plays a crucial role in the development of the granule layer of the cerebellum and stimulates the proliferation of granule neuron progenitor cells. While GIFN mice lacking STAT1 do not develop tumors, increased levels of proinflammatory cytokines and an influx of neutrophils point to an increased innate inflammatory response that likely underlies the severe neurodegenerative phenotype of these animals.

These studies indicate that IFN-receptor signaling is clearly complex, involving the coexistence of multiple JAK/STAT as well as alternative pathways. The balance in the activity of these pathways dictates the repertoire of CNS responses regulated by IFN-α. Signaling via the primary pathway involving STAT1 and STAT2 stimulates the induction of genes such as 2′5′oligoadenylate synthetase that may play a beneficial role in the CNS, for example in anti-viral defence. Moreover, the activation of this primary pathway suppresses or inhibits through unknown mechanisms, signaling via alternative type I IFN receptor-coupled signaling pathways. A reduction or loss of signaling by the primary pathway results in increased activity of the alternative signaling pathways. As the strength of the cytokine-receptor coupled signaling shifts to these alternative pathways the level and nature of the cellular response also changes which, in the case of IFN-α leads to pathogenetic responses in the CNS and thus exacerbation of disease.

Altered Expression of SOCS Influences Demyelinating Diseases in Mice

While STATs are positive regulators of cytokine signaling, SOCS act as negative regulators. The cytokine IFN-γ is produced in the CNS in the course of demyelinating diseases such as MS or EAE and has been shown to inhibit remyelination and injure oligodendrocytes. As we noted above, in EAE and cell-mediated immune responses in the GFAP-IL12 transgenic mice, there is an apparent deficit of SOCS1 or SOCS3 gene expression by oligodendrocytes. This in turn may result in increased and more prolonged cytokine activated JAK/STAT signaling predisposing these cells to adverse effects by cytokines such as IFN-γ. In support of this idea, the forced expression of SOCS1 in oligodendrocytes diminishes the responsiveness of these cells to IFN-γ and protects against damage mediated by this cytokine [7].

In contrast to IFN-γ, the cytokine leukemia inhibitory factor (LIF) ameliorates demyelination, increases the viability of oligodendrocytes and increases SOCS3 gene expression. In the cuprizone-induced demyelination model, LIF activates STAT3 signaling in oligodendrocytes resulting in increased SOCS3 expression by these cells [8]. Note that this situation contrasts with the immune-mediated models of demyelination where oligodendrocytes appear deficient for SOCS3 expression. Ultimately, by reducing LIF-activated STAT3 signaling, SOCS3 compromises the protective actions of this cytokine against oligodendrocytes. Conversely, the selective ablation of SOCS3 in oligodendrocytes significantly increases the protective actions of LIF in the cuprizone model, resulting in increased oligodendrocyte regeneration and more efficient recovery.

In all, these studies illustrate that depending on the type of cytokine and the context of the pathophysiologic state, SOCS expression can be variably regulated in neural cells such as oligodendrocytes and may have either beneficial or detrimental functions in the evolution of CNS injury and recovery from inflammatory insult.

JAK/STAT/SOCS During Inflammatory-CNS Diseases in Humans

To date little is known concerning the role of cytokines and the JAK/STAT/SOCS signaling pathways in human neuroinflammatory diseases with most information available for the autoimmune disease MS. Expression of several cytokines including IL-12, IL-6 and IFN-γ is upregulated in microglia and astrocytes of patients with active MS as compared with control patients [9]. Importantly, expression of the corresponding receptors was found on microglia but also on oligodendrocytes that form the myelin sheath and are a main target of the immune response in MS. In addition, microglia (JAK1, STAT1, STAT4), astrocytes (JAK1, STAT3, STAT4) and oligodendrocytes (JAK1, STAT4, STAT6) express JAK1 and/or STAT molecules indicating that in addition to microglia and astrocytes, oligodendrocytes can react to the inflammatory stimuli present in active MS lesions. Furthermore, in contrast to EAE, STAT3 and STAT4 were expressed by resident CNS cells in humans during MS. While this needs further clarification it could point to fundamental differences in the transcription factor content and therefore responsiveness of CNS resident cells towards cytokines in humans as compared with mice.

Therapeutic Approaches

If we assume a similar role for JAKs and STATs in human neuroinflammatory diseases as compared with experimental animal models, then drugs that affect the activity of the JAK/STAT pathway might prove to be effective therapeutics. In support of this possibility, experimental studies suggest pharmacological modulation of the JAK/STAT pathway can have a beneficial impact on the course of neuroimmune diseases such as EAE.

While several tyrosine kinase inhibitors have been developed that target specifically JAK kinase activity, effects of most of these compounds on CNS diseases has not yet been thoroughly investigated. However, from the limited data available it is clear that targeting the activity of the JAK kinases is an effective approach to suppressing EAE in rodents.

Targeting the SOCS might be another strategy to modulate the activity of signal transduction pathway activity and target cell sensitivity in CNS disease. A SOCS mimetic has been developed that mimics the effects of SOCS1 [10]. This mimetic binds to the autophosphorylation site of JAK2 and thus inhibits the activation of JAK2 and the subsequent phosphorylation of its substrates such as STAT1 (IFN-γ, TNF-α) or STAT3 (IL-6). Treatment of mice with this SOCS mimetic can reduce the incidence of EAE significantly but also is effective in ameliorating symptoms when given after onset of clinical symptoms.

Final Discussion

Similar to peripheral organs, inflammatory stimuli affecting the CNS induce the local production of a variety of cytokines that orchestrate the host response. For many cytokines binding to their cell surface receptor is coupled to the activation of the JAK/STAT/SOCS signaling cascade as well as other signal transduction pathways. Further complexity is introduced due to the cell-specific localization of specific molecular components of these pathways. Achieving coherent, balanced and specific cytokine signaling is the culmination of multiple levels of control with cross-talk between individual pathways as well as direct regulatory inputs that further modulate the duration of signaling. Disruption in this balance can produce undesirable consequences as bias towards an individual signal pathway can lead to inappropriate cellular responses and cause damage or retard repair and regeneration within the CNS. Therefore, altered cytokine signal transduction may contribute to the pathogenesis of certain neurological diseases. In this regard, it is significant that there are environmental agents such as viruses as well as genetic determinants that are known to interact directly with the signal transduction networks for many cytokines altering signaling thresholds that in turn can lead to an inappropriate cellular response. Achieving a thorough understanding of the dynamics and consequences of the signaling mechanisms in the CNS for individual cytokines is therefore an important goal that could lead to more effective therapeutic strategies for the treatment of adverse neuroinflammatory diseases.

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Central Neuropathic Pain

►Central Pain

Central Nucleus

Definition

The main subdivision of the inferior colliculus that receives most inputs ascending from the lower auditory system in the brainstem. It projects to the ventral division of the medial geniculate body.

►Inferior Colliculus

Central Pain

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Synonyms

Thalamic pain; Deafferentation pain; Central neuropathic pain

Definition

The International Association for the Study of Pain (IASP) defines neuropathic pain as "Pain initiated or caused by a primary lesion or dysfunction of the peripheral or central nervous system." A new classification is being introduced by a working group on Neuropathic pain. According to this working group, it is suggested that neuropathic pains are pains arising as a direct consequence of a lesion or disease affecting the somatosensory system. This revised definition fits into the nosology of neurological disorders and also distinguishes neuropathic pain from normal physiological plasticity seen when the somatosensory system is activated following noxious stimulation.

Central Pain (CP) occurs following lesions of the sensory pathways in the spinal cord or brain. The essential pathological feature is a lesion in the CNS resulting in partial or complete loss of sensory input in the nervous system with corresponding negative sensory phenomena, such as partial or complete anesthesia in the area subserved by the structure with the lesion [1]. In parallel with loss of input, ectopic activity, regeneration and disinhibition may take place resulting, in some cases, and with variable risk among different etiologies, in secondary development of hypersensitivity. A key issue in diagnosing CP is a detailed pain history and thorough neurological examination that should include a careful sensory examination, evaluating decreased or increased responses to touch, vibration, pinprick, and thermal stimuli as well as a mapping of the distribution of the sensory dysfunction (see also ►Neuropathic Pain).

Characteristics

Etiology

A variety of diseases may give rise to CP (Table 1). The most common and well described central pains are central post-stroke pain and CP in spinal cord injury and ►multiple sclerosis, but any lesion along the sensory neuraxis from the dorsal horn to the brainstem, thalamus, subcortical white matter and probably

Central Pain. Table 1 Etiology of central neuropathic pain

Infarction or hemorrhage of brain or spinal cord
Multiple sclerosis
Syringomyelia or syringobulbia
Neoplasm of brain or spinal tissue
Spinal cord injury
Parkinson's disease
Epilepsy
Inflammation of brain or spinal cord tissue

cortical areas may cause CP [1]. Patients with ►Parkinson's disease, which is dominated by rigidity, bradykinesia and tremor, may also experience pain and sensory disturbances, but some of these pains may be related to dystonia and fluctuations in anti-parkinsonian medication [1]. Patients with ►epilepsy may have pain as part of a seizure or aura [1].

Symptoms and Signs in CP

Central pains are characterized by a specific lesion or disease of the CNS and

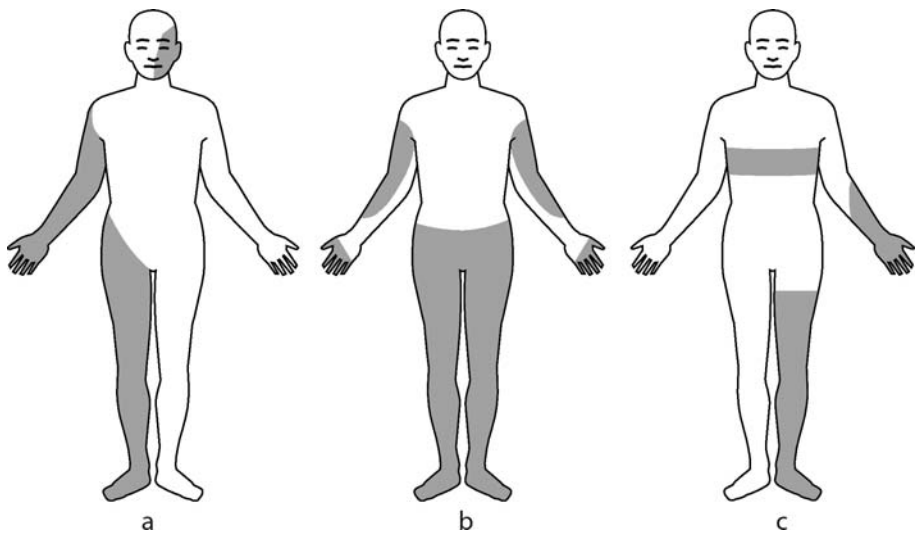
- Pain located in a neuroanatomical area with partial or complete sensory loss.
- Spontaneous ongoing or paroxysmal pain (stimulus independent).
- Stimulus evoked pain (stimulus dependent), including for example touch-evoked or cold ►allodynia, ►hyperalgesia, abnormal summation of pain and after-sensations.

These symptoms/signs may occur in various combinations, but do not necessarily have to be present altogether. The underlying disease itself may also influence the pain and sensory pattern and contribute to heterogeneity of the core phenomena of CP.

Stimulus-independent pains are spontaneous pains and can be either continuous or paroxysmal. The character differs, but shooting, shock-like, aching, cramping, crushing, burning types of pain are descriptors that have been used. The pain may be described as superficial or deep or both. Other sensations such as ►paraesthesia and ►dysaesthesia may be present spontaneously or evoked (e.g., ongoing tight or tingling sensations evoked by touching the area). The onset of CP varies, but in most cases patients develop CP within three to six months after their central nervous system lesion. Any delayed onset of neuropathic pain should prompt an examination for other causes (e.g., syringomyelia in cases of spinal cord injury). After a ►stroke, CP may be distributed in a hemi body fashion or it may affect a smaller part of one side with sensory disturbance (e.g., part of a limb). In lateral medullary ►infarction, the symptoms may be crossed with pain in one side of the face and the other side of the rest of the body (Fig. 1).

In spinal cord injury, pain may be located at the level of injury as a band around the thorax, or below the level of injury, either diffusely or in patches (Fig. 1), while in syringomyelia, pain is often distributed in a segmental pattern. In multiple sclerosis, both hemi body pain and bilateral pain may occur (Fig. 1). Many patients report that the pain is increased by changes in weather, cold, psychological factors like stress or changes in mood.

Stimulus-dependent pains are classified according to the stimulus modality that provokes them (i.e., mechanical, thermal or chemical). Evoked pain is a common feature of CP patients [1–7]. Evoked pain is often present within the area of spontaneous pain, but may extend beyond this area or be present in patients without spontaneous pain. In spinal cord injury, patients may experience evoked pain below the level of injury in cases of incomplete spinal cord injury or in the border zone at the level of injury. There seems to be a correlation between evoked pain felt at the level of injury and spontaneous pain below the level of injury [4].



Central Pain. Figure 1 Examples of distribution of central pain in a patient with central post-stroke pain following a lateral medullary infarction (a), a patient with at- and below level neuropathic pain in spinal cord injury (b), and a patient with central pain following multiple sclerosis (c).

The most common and important forms of stimulus-dependent pains include allodynia, which implies that stimuli which normally do not provoke pain now do so. Allodynia may coexist with hyperalgesia. Non-noxious brush, touch or thermal stimuli are examples of stimuli that can give rise to allodynia. Allodynia may be present with little impact on the patient's daily life; in other cases, it is the dominating clinical feature and very disabling. The touch from cloth or taking a shower may cause intense pain, and a gentle touch may be felt as a burning sensation. While allodynia usually is considered to be a cutaneous phenomenon, recent observations suggest the presence of a deep tissue allodynia. For example, in post-stroke pain, movement-induced pain has been described and deep pain may be associated with a lowering of pain threshold to mechanical pressure. Allodynia to touch is best assessed using cotton wool or a small brush and is assessed by brushing the skin lightly. This may elicit a burning pain sensation in patients with dynamic mechanical allodynia but also non-painful dysaesthesia. Allodynia to cold and warm stimuli may be assessed using thermo-rollers. In cases of pinprick hyperalgesia, the patient will report increased pain compared to the mirror site when pricked on the skin with a pin. After-sensations with continued pain long after the stimulation has ceased may be observed [see also Neuropathic Pain].

Sensory Deficits and CP

An essential part of neuropathic pain is loss of sensory function. In some cases, sensory changes are subtle and a thorough sensory examination is needed, including perhaps the use of quantitative methods. Abnormal temperature and pain sensibility is the most consistent abnormality in post-stroke pain and it is suggested that a spino-thalamo-cortical sensory deficit is a necessary, albeit not a sufficient condition for the occurrence of CP [2–4]. The sensory deficit may be dissociated from a decrease in thermal and pinprick sensations and a relative preservation of vibration and other somatosensory functions. In addition to the sensory deficits, some patients may have a paradoxical sensitivity to cold and heat such that cold is perceived as hot and vice versa.

Epidemiology of CP

There is limited information on the frequency of CP. In a prospective study that included 207 consecutive stroke patients, 8% developed CP within the first year after their stroke [2]. Lesions of the thalamus and lateral medullary infarction are associated with higher risks of developing CP. Multiple sclerosis pain is likewise frequent [6], and Österberg et al. reported that 28% of patients with multiple sclerosis have CP [7]. In spinal cord injury, CP occurs in about 30–45% [8]. Pain at the level of injury seems to have an early onset, while CP below the level of injury may develop later after the spinal injury. Both types of pain tend to persist despite attempts at management [8]. Although some studies have indicated a higher incidence of CP in patients with incomplete lesions, other studies suggest that there is no relationship between the extent or site of spinal lesion and the presence of pain. Older age at time of injury has been found to be related to spinal core injury neuropathic pain.

Mechanisms of CP

The mechanisms responsible for CP are still unclear, but various theories have been advanced to explain these pains. The frequent incidence of evoked pain and decreases in mechanical thresholds in painful areas suggest the presence of hyperexcitability, and clinical and experimental studies indicate the presence of sensitization of 2nd or 3rd order neurons in the CNS that have lost their normal patterned input [3]. After a central nervous system lesion, several changes, including release of glutamate, up-regulation of sodium channels, activation of glia and loss of inhibition, are thought to increase the excitability of central neurons from which abnormal input may arise. In addition, the thalamus is thought to play a key role in CP [3] and bursting activity and reorganization has been demonstrated in the thalamus following central lesions. Disinhibtion due to partial lesions and imbalance between pathways has also been suggested to contribute to the development of CP. Among the more interesting recent theories, Craig has suggested that CP is due to loss of a normal inhibitory effect exerted by cool-signaling pathways from lamina I projecting to the thalamus and insula [9]. According to this hypothesis, a lesion of the lateral cool projection system disinhibits the medial system of heat-pinch-cold neurons passing from Lamina I to the medial part of the thalamus. This disinhibition results in a release of cold allodynia, burning and ongoing pain [9]. Disruption of thermo-sensory integrations leads to a disinhibition of thalamocortical neurons that respond to noxious inputs and a sensation of burning pain [9].

Treatment of CP

Like other chronic pain conditions, CP is a complex psychological experience which may have consequences for daily activities, sleep, cognition, emotion, behavioral and social relations and a broad approach to the treatment is essential. There is limited data on the pharmacological treatment of CP. Gabapentin, pregabalin, tricyclic antidepressants, lamotrigine and cannabinoids are treatments that have been shown to relieve CP, but other drugs like serotonin-noradrenaline reuptake inhibitors and opioids have not yet been studied in CP conditions [10]. Gabapentinoids and antidepressants are often considered first drugs of choice, but as in other neuropathic pain conditions these drugs, even when given in effective and tolerable doses, only reduce pain to a variable extent and

other drugs or drug combinations may be considered. Patients with CP often have concurrent medical problems and impairment, are treated with multiple drugs with unwanted side-effects, and they may be elderly, which should be considered when treating CP.

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Central Pattern Generator

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Synonyms

Neural pattern generator; Neural oscillator

Definition

A central pattern generator (CPG) is an assembly of neurons that possesses the ability to produce a rhythmic activity pattern without phasic sensory feedback information. The rhythm generating ability can be due to either endogenous bursting properties within individual neurons (Pacemaker-driven CPGs) or synaptic interactions between neurons (►Network Oscillators).

Characteristics

Peripheral Versus Central Control Debate

The concept of central pattern generation was introduced in the early part of the twentieth century to account for experiments which demonstrated that deafferented hind limbs in anaesthetized cats were still able to produce rhythmic movements/muscle contractions [1]. This observation suggested that the rhythmic pattern of alternating contractions of flexor and extensor muscles underlying limb movements during locomotion are generated centrally within the spinal cord without the requirement of sensory feedback from the contracting muscles.

This "central control hypothesis" contradicted the "peripheral control hypothesis" of locomotion that was prevalent at the time. The "peripheral control hypothesis" considered the reflex as the basic functional unit in the nervous system and proposed that rhythmic movements (e.g. walking, swimming) are caused by the activation of alternating reflexes, i.e. contraction of a flexor muscle causes the activation of a reflex that triggers contraction of the antagonistic extensor muscle, which in turn activates the reflex that causes contraction of the flexor muscle leading to rhythmic movements. Furthermore, it was thought that the sequential activation of individual reflexes, where the action of one reflex causes a sensory response that triggers a second reflex and so on (►Reflex Chain), also underlies the control of complex behavioral sequences.

Based on a wide range of studies in both invertebrates and vertebrates this debate has been settled in favor of the central control hypothesis and the CPG has emerged as a general principle of neuronal organization. However, it has also been recognized that phasic sensory feedback has an important role to play in shaping CPG output.

It should be noted that CPGs do not only generate rhythmic activity that directly controls motor behaviors, but that they also play a role in CNS activity patterns that are believed to be important for cognitive functions (e.g. hippocampal gamma and theta rhythms [2]). However, this essay concentrates on motor pattern generation as it has proved particularly useful to study the organization and function of CPGs.

Mechanisms of Central Pattern Generation

Mechanisms for the generation of rhythmic activity in CPGs have frequently been divided into two broad categories – pacemaker-driven CPGs and ►neuronal network oscillators. Pacemaker-driven CPGs rely on neurons with intrinsic bursting properties (►Intrinsic properties), so called ►endogenous bursters, for their

rhythm generating ability (Fig. 1a). The inherent ability of endogenous bursters (pacemaker) to generate rhythmic membrane potential oscillations that drive bursts of activity is due to the specific interplay between various ion channels. Most commonly, the sustained depolarization of the membrane potential during a burst, a so called ►plateau potential, is caused by voltage-activated persistent Na^+ currents, voltage-activated Ca^{++} currents or the activation of NMDA receptors. Calcium-dependent K^+ currents or slow I_A currents are the most common channels responsible for the termination of the plateau potential and the repolarization of the membrane potential. The activation of a hyperpolarization-activated slow depolarizing current I_h by the repolarization at the end of the burst is frequently responsible for the initiation of the next burst. In some pacemaker neurons, so called ►conditional bursters, the bursting property is dependent on the action of modulatory neurotransmitters (e.g. serotonin, dopamine).

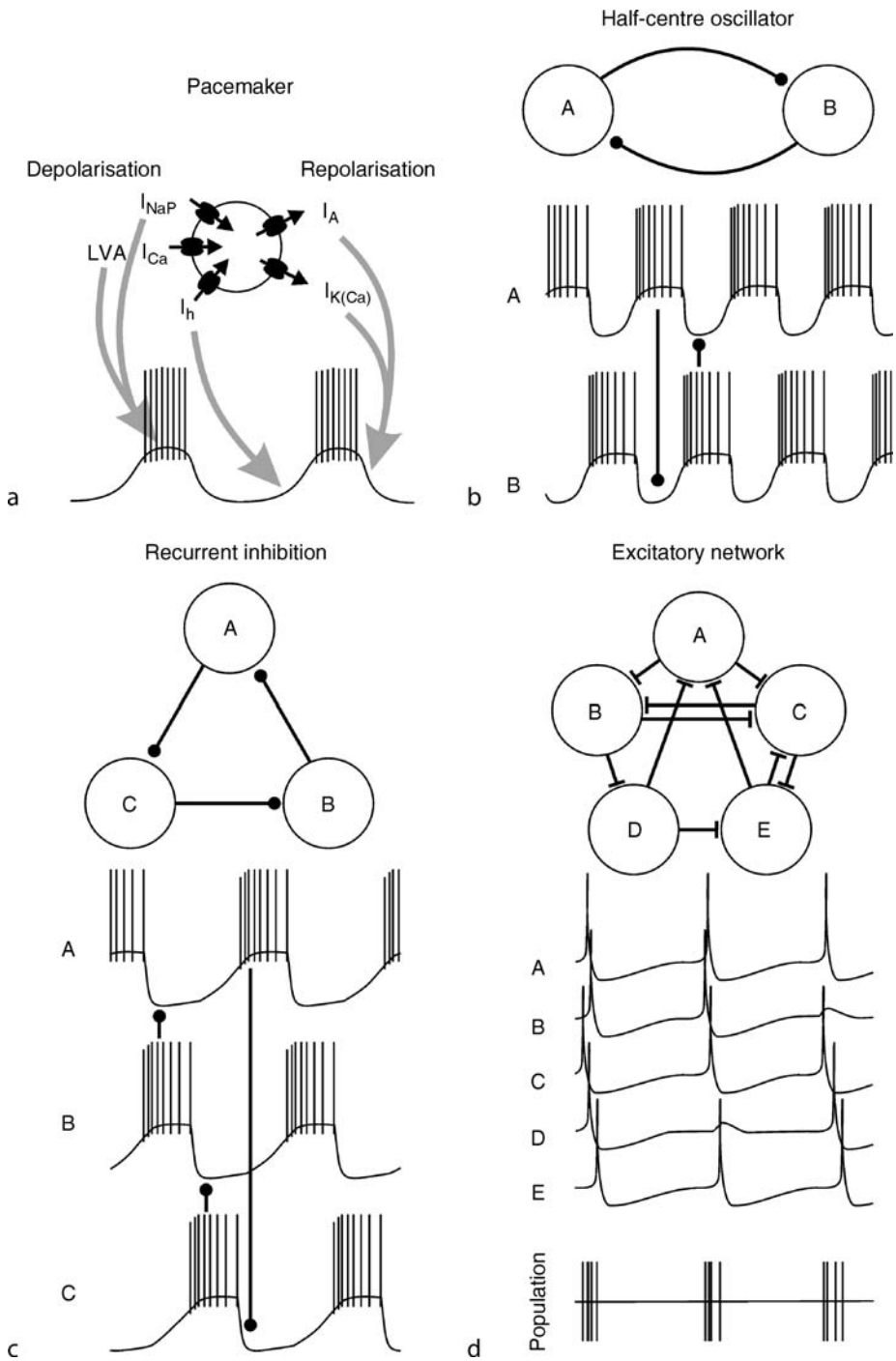
In contrast to pacemaker-driven CPGs, the rhythm generating property of network oscillators is an emergent network property based on the synaptic connections between neurons that form a CPG. The ►half-centre oscillator, first proposed by Graham Brown [1], is arguably the most successful model of a ►network oscillator (Fig. 1b). This neuronal network owes its rhythm generating ability to reciprocal inhibitory synaptic connections between two antagonistic neurons or populations of neurons; the "►half-centers." In addition, the neuronal network requires restorative mechanisms that will limit the reciprocal inhibitory effects to enable rhythmic switching of activity in the two half-centers. This can be spike frequency adaptation, activity-dependent synaptic depression, or some other mechanism that results in an activity-dependent reduction of the inhibitory effect. Tonic excitation of the CPG triggers activity in one half-centre, which consequently suppresses activity in the second half-centre. The restorative mechanisms will enable the suppressed half-centre to escape from the inhibition, which will inhibit the first half-centre causing the switch of activity between the two half-centers. Thus, the two half-centers produce an alternating two phase rhythm. If the two half-centers possess ►post-inhibitory rebound properties, they can sustain prolonged bursting activity in the absence of a tonic command signal. Here rebound from the inhibition caused by activity in the antagonistic half-centre can be sufficient to initiate a new burst of activity. A neuronal network consisting of three neurons/neuron populations with recurrent inhibitory connections (Fig. 1c) can be seen as an extension of the half-centre oscillator that produces a three phase activity pattern. This type of CPG does not require any specific restorative mechanism as one neuron is always in the recovery phase; e.g. whilst neuron A is active, neuron C is inhibited allowing neuron B to recover; when neuron B starts to fire it will inhibit neuron A allowing neuron C to recover, and so on.

Both *in vitro* experiments and theoretical modeling studies have shown that ►neuronal networks connected solely by excitatory connections can also produce rhythmic activity patterns without the need for pacemaker neurons [2]. In these ►bistable networks, fast excitatory interactions synchronize the activity within a group of neurons causing a population burst of activity, whilst the inter-burst interval is determined by the inter-spike interval in the individual neurons (Fig. 1d). These models can account for the observed rhythm generating properties in isolated spinal cord preparations after complete block of inhibitory synaptic connections.

Studies in a wide variety of vertebrate and invertebrate preparations have shown that most CPGs do not rely on a single mechanism for rhythm generation, but use a combination of mechanisms and should be considered as hybrid CPGs. For example, the leech heart CPG was considered a half-centre oscillator, but it has now been recognized that leech heart interneurons also possess intrinsic pacemaker properties [3]. Endogenous bursting neurons are important for the rhythm generating properties in one of the best understood CPGs, the pacemaker-driven pyloric network located in the crustacean stomatogastric ganglion. However, synaptic network interactions also contribute significantly to the pyloric rhythm [4]. Similarly, the mammalian respiratory CPG located in the Preboetzinger complex appears to rely on a combination of interneurons with pacemaker properties and excitatory connections that form an excitatory network oscillator for its rhythm generating ability [5]. Excitatory network oscillators have also been proposed to underlie rhythm generating abilities within the mammalian spinal hemicord when inhibitory connections are blocked [2]. However, left-right coordination in the mammalian spinal cord is organized by a half-centre oscillator. Modeling studies have clearly shown that the combination of multiple pattern generating mechanisms helps to stabilize and enhance the robustness of the rhythm generating ability of a CPG. It can also increase the dynamic range of a CPG and introduces a degree of redundancy to the neuronal network.

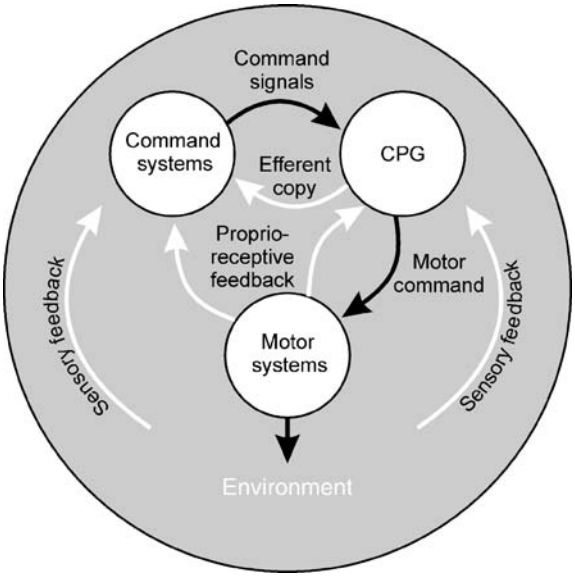
The Role of Sensory Feedback in Motor Pattern Generation

Most insights into the rhythm generating mechanisms of CPGs have been derived from *in vitro* experiments using isolated nervous system preparations that were completely deprived of sensory information. Whilst these experiments have proved extremely useful to demonstrate that the basic rhythm generating properties do not require sensory information, they ignore the role of sensory feedback in rhythm generation. However, in



Central Pattern Generator. Figure 1 Diagrams of various CPG rhythm generating mechanisms. (a) Pacemaker CPG. The upper diagram shows various ion channels that commonly underlie the endogenous bursting property in pacemaker neurons (I_{Nap}: persistent Na^+ current, LVA I_{Ca}: low-voltage activated Ca^{++} current, $I_{K(Ca)}$: Ca^{++}-dependent K^+ currents, I_A:slow activating K^+ currents, I_h:hyperpolarisation-activated inward currents). The lower trace shows a schematic representation of the electrical activity pattern in a pacemaker neuron. The grey arrows indicate which ion channels are responsible for the different phases of the bursting pattern. (b-d) Schematic representations of the network configurations and activity patterns of three types of network oscillators. The diagrams at the top of each panel shows the connectivity between the network elements. Circles denote inhibitory synapses, whilst bars denote excitatory synapses. The traces below the diagrams show the activity pattern inthe correspondingly labelled network elements. See text for more details.

the intact animal CPGs do not operate in isolation but receive constant inputs from peripheral sense organs and proprioreceptors (Fig. 2). The influence of sensory feedback on pattern generation is obvious in locusts where removal of phasic sensory feedback from wing proprioreceptors significantly reduces wingbeat frequency. The natural burst frequency of the flight CPG can be restored by electrical stimulation of afferent sensory fibers in phase with the CPG activity pattern [6]. Similarly, sensory feedback significantly influences the rhythmic activity in the lamprey swim CPG as can be demonstrated by alternate bending of the caudal segments to simulate natural swimming movements. This activates stretch receptors along the spinal cord that can entrain the internal locomotor rhythm generated by the swim CPG to the frequency of the external movements [7]. Extensive evidence also exists for an important role of sensory feedback in mammalian locomotion. Overall sensory feedback appears to fulfill three main functions. Firstly, it can provide a corrective signal to adapt CPG activity to changes in an unpredictable environment as is necessary for the accurate step placement in a rough terrain or the adjustment of a wingbeat in a turbulent air stream. Secondly, sensory feedback can provide timing cues about ongoing activity resulting in the stabilization of the pattern. For example, stepping movements in cats become more variable in the absence of sensory feedback [7]. Similarly, mechanosensory feedback from the lips reduces the variability of bite intervals in the pond snail *Lymnaea* [8]. Thirdly, sensory feedback provides information about the position of the body or a limb within space which is important for adapting and planning further movements. Thus, in most systems central pattern generating mechanisms and sensory feedback mechanisms are closely integrated and interact to produce a robust rhythmic activity pattern that can be rapidly adjusted to cope with unpredictable environmental disturbances.



Central Pattern Generator. Figure 2 Diagram of interactions between command systems, CPGs, motor systems and the environment. CPGs need to be considered in the context of the entire organism and its interaction with the environment to fully understand their function. Whilst CPGs can generate a basic motor pattern, this pattern is influenced by command and modulatory signals from higher order command systems as well as feedback from the motor system and the environment. Black arrows: command signals, white arrows: feedback signals.

Command Systems, Modulation and Behavioral Choice

CPG driven activity patterns can be active continuously throughout the life of an organism (e.g. mammalian respiration) or can be short episodic events triggered by a specific stimulus (e.g. fish escape response). The study of command systems that drive CPG activity has concentrated particularly on well-defined, robust episodic behaviors in relatively simple preparations that are reliably triggered by a specific stimulus. These preparations promised the possibility of identifying specific neurons, so called ▶command neurons that can trigger a specific CPG activity/behavior. The definition of what actually constitutes a ▶command neuron has been intensely debated and it has been proposed that only neurons that are both sufficient and necessary for the initiation of a specific behavior should be considered command neurons [9]. However, very few neurons actually fulfill these stringent criteria. Whilst there are a range of neurons, in particular in invertebrates, that fulfill the sufficiency criteria (e.g. slow oscillator and some cerebral buccal interneurons for activating the feeding CPG in molluscs such as *Lymnaea* and *Aplysia*, the Mauthner cell for the escape behavior in fish, etc.), very few also fulfill the necessity criteria (e.g. the dorsal ramp interneuron for activating escape swimming in the marine mollusc *Tritonia*).

This observation is consistent with the recognition that CPG activity can be driven by different stimuli and that there are usually parallel pathways that all contribute to the activation of a CPG. Thus, it is not surprising that most neurons that can drive a CPG do not appear to be absolutely necessary to trigger activity in a specific CPG. Furthermore, CPGs are flexible and can generate different activity patterns depending on the precise nature of the stimulus and an organism's requirements. Whilst the different patterns utilize the same muscle groups, motoneurons and CPG interneurons, the sequence and phase relationship of activation of these elements can differ. For example, the

Aplysia feeding CPG can produce ingestive and egestive motor patterns. These different patterns can both be driven by activity in the cerebral-buccal interneuron 2 (CBI-2). However, if CBI-2 is activated on its own the elicited feeding pattern is more ingestive-like, whilst co-activation of CBI-2 together with CBI-3, a second cerebral-buccal interneuron produces a more egestive-like activity pattern [10]. There are now many examples of modulatory interneurons that can affect the pattern of CPG activity. Some of the most striking and best characterized examples of network reconfigurations by the action of neuromodulators and higher order interneurons have been provided by studies of the pyloric and gastric mill CPGs in the crustacean stomatogastric nervous system. Here, it has been analyzed in great detail how different neuromodulators can alter CPG activity, how individual CPG interneurons can switch between different CPGs, and how higher-order interneurons can cause the complete reconfiguration of CPG networks to produce different activity patterns [4]. Thus, CPGs are not hard-wired, but dynamic ►polymorphic networks that can be reconfigured by the action of higher order interneurons, which are part of a general command system. This is clearly considerably more efficient than individual hard-wired CPGs for different behaviors (e.g. walking, running and jumping in mammals). Furthermore, the inherent flexibility in the CPGs and command systems that drive CPG activity provides the basis for behavioral choice as it enables motor patterns to be chosen for and adapted to specific requirements.

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Central Regulation of Autonomic Function

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Definition

The central regulation of autonomic function depends on structures distributed throughout the neuraxis. They include the ►insular cortex, ►anterior cingulate cortex, ►amygdala, ►hypothalamus, ►periaqueductal gray matter (PAG) of the midbrain, ►parabrachial nucleus in the dorsolateral pontine tegmentum, and several areas of the medulla, including the ►nucleus of the solitary tract (NTS), reticular formation of the ventrolateral medulla (VLM) (►Ventrolateral medullary reticular formation) and medullary raphe nuclei [1–3]. These areas are reciprocally interconnected, receive converging visceral and somatosensory information, and their activity is modulated according to the behavioral state of the individual, including the sleep-wake cycle. These areas control, directly or indirectly, the activity of preganglionic sympathetic or parasympathetic neurons, and generate stimulus-specific patterns of autonomic output critical for homeostatic reflexes and integrated responses to emotion, stress, or other stimuli [2].

Characteristics

Description

The insular cortex is the site of cortical representation of visceral, pain, and temperature sensation [2]. Nuclei in the ventromedial portion of the thalamus relay these sensory modalities to the insula. This cortical area is connected to the amygdala, lateral hypothalamus and brainstem autonomic nuclei, and is also interconnected with the anterior cingulate and ventromedial prefrontal cortices. The anterior cingulate cortex has a major role in regulation of affective behavior, and modulation of bodily arousal via the autonomic nervous system [4]. It has extensive connections with the prefrontal cortex, amygdala, hypothalamus, and brain stem and receives thalamic inputs involved in arousal and relay of nociceptive information.

The amygdala nuclear complex attaches emotional significance to sensory stimuli, including pain, and initiates the autonomic responses associated with emotion, including fear [5]. The amygdala receives inputs from all sensory modalities via projections from the brainstem, thalamus, and association areas of the cerebral cortex. The central nucleus of the amygdala is the effector structure of the amygdala complex and projects to the hypothalamus and brain stem areas involved in autonomic, endocrine, and motor expression of emotional responses [5].

The hypothalamus has a central role in the integration of autonomic and endocrine responses required for homeostasis and adaptation to internal or external stimuli. It is subdivided functionally into a periventricular zone, involved in circadian and neuroendocrine control, a medial zone involved in control of foraging behavior, and a lateral zone controlling arousal and motivated behavior. Several hypothalamic nuclei innervate brain stem and spinal targets controlling sympathetic and parasympathetic neurons. These include the ►paraventricular nucleus (PVN), the dorsomedial nucleus, the arcuate (infundibular) nucleus, and the posterior lateral hypothalamus (perifornical region) [1–2].These hypothalamic regions contain separate populations of neurons that project to different subsets of preganglionic neurons to generate distinct patterns of autonomic response according to specific stimuli.

The PAG consists of different longitudinal columns that receive specific inputs from sensory pathways, hypothalamus, and cerebral cortex and initiate stimulus-specific autonomic, somatic, and antinociceptive responses to external stressors [6]. The parabrachial nucleus, located in the dorsolateral pontine tegmentum, is a major relay center for converging visceral, nociceptive, and thermoreceptive information to the forebrain and contains separate subnuclei involved in taste, salivation, gastrointestinal activity, cardiovascular activity, and respiration [2,3]. The NTS is the first relay station for taste and general visceral afferents in the brainstem and conveys this information to all central autonomic regions, both directly and via the parabrachial nucleus. The NTS is also critically involved in all medullary reflexes controlling cardiovascular, respiratory, and gastrointestinal functions [3,7,8].

The VLM contains neurons that control sympathetic vasomotor tone, cardiac function, respiration, and endocrine function [3,7,8]. The rostral VLM contains glutamatergic neurons that provide the major tonic excitatory input to the sympathetic preganglionic vasomotor neurons and mediate most descending and reflex influences controlling arterial pressure. Epinephrine synthesizing C1 neurons of the rostral VLM contribute to this glutamatergic input and are required for sympathoexcitatory reflexes. The caudal VLM contains GABAergic neurons that, via their projections to the rostral VLM, mediate the baroreflexes and other sympathoinhibitory reflexes. Norepinephrine synthesizing A1 neurons of the caudal VLM project to the hypothalamus and participate in control of endocrine function, including secretion of arginine vasopressin. The medullary raphe contains serotonergic neurons that project to the spinal cord and control nociceptive, sympathetic, and respiratory functions. Medullary raphe-spinal pathways are involved in thermoregulatory responses, including skin vasoconstriction [2,3].

Higher Level Structures

The insular and anterior cingulate cortices, amygdala, hypothalamus, and PAG form a functional unit that has a critical role in integrated responses to stress, emotional responses, and motivated behavior [1,4,5,6]. These areas receive and integrate inputs from several sources. Inputs from visceral receptors, nociceptors, and thermoreceptors reach these areas via both the dorsal horn and the NTS. The dorsal horn receives inputs from the dorsal root ganglia and projects via spinothalamic and spinobulbar pathways [2]. The NTS relays inputs from taste receptors, baroreceptors, chemoreceptors, pulmonary, and gastrointestinal receptors, carried via the facial, glossopharyngeal, and particularly the vagus nerves [2,3]. Both the dorsal horn and the NTS project to the parabrachial nucleus, hypothalamus, and amygdala, as well as to the thalamus, which then relays visceral inputs to the insular and anterior cingulate cortices [2]. At all these levels, there is integration of visceral with pain and temperature sensations. Humoral information, including levels of circulating peptides such as angiotensin II or cytokines, reaches the central autonomic structures in part via the circumventricular organs, which lack a blood brain barrier. These include the area postrema at the level of the fourth ventricle, and the subfornical organ and vascular organ of the lamina terminalis at the level of the anterior wall of the third ventricle [1]. The central autonomic structures, either directly or via the hypothalamus, receive influences from the suprachiasmatic nucleus (circadian pacemaker), the limbic cortical areas, and the cholinergic and monoaminergic cell groups involved in behavioral arousal and regulation of the sleep-wake cycle.

The NTS, VLM, and medullary raphe are involved in autonomic reflexes and mediate the effects of rostral areas, including the amygdala, hypothalamus, and PAG, on sympathetic and parasympathetic outflow [3,7,8]. The medullary cardiovascular and respiratory reflexes have several features in common. Baroreceptor, cardiac receptor, chemoreceptor and pulmonary mechanoreceptor afferents provide an excitatory input to the NTS that via direct and indirect propriobulbar connections, activate or inhibit the sympathoexcitatory neurons of the rostral VLM, vagal neurons of the

nucleus ambiguus or dorsal vagal nucleus, and the neurons of the ventral respiratory group [3,7,8].

Lower Level Components

The preganglionic sympathetic or parasympathetic neurons are the final central effectors of the forebrain and brainstem structures controlling autonomic output [2]. The sympathetic preganglionic neurons are located primarily in the intermediolateral cell column at T1–L2 levels of the spinal cord and are organized into different functional units that specific targets via the paravertebral ganglia, prevertebral ganglia, or adrenal medulla. The sympathetic outflow is critical for responses to stress, such as hypoglycemia or hemorrhage, control of arterial blood pressure, and thermoregulation. Descending pathways from the hypothalamus and brain stem exert a differential influence on the different populations of sympathetic preganglionic neurons so that there is patterned activation of preganglionic outflow according to the physiological needs. For example, the rostral VLM activates muscle and splanchnic vasoconstrictor preganglionic neurons for maintenance of arterial pressure, whereas the medullary raphe controls skin vasomotor preganglionic neurons related to thermoregulation [2,3].

The vagus nerve provides the most widespread cranial parasympathetic output. Vagal preganglionic neurons are located in the dorsal motor nucleus, which controls respiratory and abdominal viscera, and in the ventrolateral region of the nucleus ambiguus, which innervates the heart. The vagus has a critical role in beat-to-beat control of the heart rate and regulation of gastrointestinal motility and secretion [3]. The sacral parasympathetic outflow arises from the sacral parasympathetic nucleus, located at the S2-S4 segments of the spinal cord, and is critical for micturition, defecation, and penile erection.

Function

The anterior cingulate cortex and the amygdala control autonomic responses associated with motivated behavior and emotion. The human anterior cingulate cortex is activated during goal-directed behaviors associated with sympathetic activation [4]. Stimulation of the anterior cingulate cortex elicits increases or decreases in blood pressure, heart rate or respiration; mydriasis; piloerection and facial flushing; salivation; nausea or vomiting; and bowel or bladder evacuation. The amygdala receives inputs from all sensory modalities, both directly via the thalamus or parabrachial nucleus, and indirectly after cortical processing in association areas, particularly the insula and anterior temporal cortex [5]. In humans, the amygdala is activated by exposure to emotionally arousing stimuli, passive viewing of facial expressions (particularly fear), and \conditioned aversive stimuli. Together with the orbitomedial prefrontal cortex, the amygdala is critical for emotional and decision making on the basis of previously experienced sensations. The central nucleus of the amygdala is the effector structure for emotional responses. Both directly or via the bed nucleus of the stria terminalis, it innervates the hypothalamus, PAG, NTS and VLM, which initiate sympathoexcitation, release of stress hormones, and motor responses, including startle and vocalization [5].

The hypothalamus is critical for integration of autonomic with endocrine and behavioral responses required for homeostasis and adaptation [1,2,9,10]. The hypothalamic autonomic nuclei receive direct input from the anterior cingulate cortex, insula, and hippocampal formation, amygdala, and basal forebrain, as well as ascending inputs from the NTS, parabrachial nucleus, and A1/C1 catecholaminergic neurons of the VLM. The PVN provides the most widespread autonomic output of the hypothalamus and is crucial for coordinated endocrine and autonomic responses to stress [9]. Different neuronal subpopulations of the PVN, including the magnocellular neurons that secrete AVP to the general circulation, the parvocellular neurons that synthesize corticotrophin releasing hormone and activate the pituitary-adrenocortical axis, and the neurons projecting to autonomic nuclei of the brain stem and spinal cord, are activated, in a stimulus-specific fashion, by hypoglycemia, hypovolemia, cytokines, pain, and environmental stressors [2,9]. An important group of neurons in the posterior lateral hypothalamus synthesize hypocretin (also called orexin) and provide widespread projections to the hypothalamus, brain stem, and spinal cord. Via these projections, the hypocretin/orexin neurons prevent abrupt transitions between wakefulness and sleep, promote food intake and regulate sympathetic function [10].

The PAG is a critical component of the circuits involved in emotion and stress responses, including those triggered by pain [6]. The different columns of the PAG receive specific inputs and generate stimulus-specific responses. The lateral column of the PAG, which receives well-localized cutaneous nociceptive inputs, initiates flight-or-flight responses characterized by sympathetic activation with hypertension and tachycardia and blood flow redistribution to the face (fight) or lower limbs (flight) responses; these responses are associated with opioid-independent analgesia. In contrast, the ventrolateral PAG, which receives poorly localized somatic, visceral, and muscle inputs, elicits hypotension, bradycardia, immobility, and hyporeactivity to the environment; this is associated with opioid-dependent analgesia. The lateral and ventrolateral columns of the PAG provide descending inputs to different targets in the VLM and ventromedial medulla, which mediate both the cardiovascular and pain-modulatory responses [6].

The rostral VLM has a critical role in tonic maintenance of arterial blood pressure [7]. Medullary reflexes are critical for control of the blood pressure,

heart rate, respiration, and gastrointestinal function [3,7,8]. A typical example is the baroreceptor reflex (baroreflex), which provides a powerful moment-to-moment negative feedback regulation of arterial pressure that minimizes the fluctuations of arterial pressure during standing, exercise, emotion, and other conditions. An increase in arterial pressure activates mechanosensitive baroreceptor terminals in the carotid sinus and aortic arch. Baroreceptor afferents excite neurons in the NTS that (i) directly activate the cardiovagal neurons in the nucleus ambiguus (leading to a decrease in the heart rate; (ii) via GABAergic neurons in the caudal VLM, inhibit the sympathoexcitatory neurons of the rostral VLM controlling vasomotor tone in muscle and visceral blood vessels (resulting an a decrease in total peripheral resistance); and (iii) via polysynaptic pathways, inhibit AVP release from the hypothalamus. Unloading of the baroreceptors, as occurs during standing, elicits opposite responses vasoconstriction and tachycardia) [3,8]. Vasoconstriction of muscle and splanchnic blood vessels is critical to prevent orthostatic hypotension.

Pathology

The central control of autonomic functions can be affected by focal or degenerative disorders. Ischemic stroke involving the insular cortex can produce cardiac arrhythmias, which are a potential cause of sudden death Limbic seizures arising from the amygdala or anterior cingulate cortex may produce cardiac arrhythmias, cutaneous vasomotor and sudomotor changes, mydriasis, vomiting, or respiratory manifestations. Hypothalamic disorders are commonly associated with disturbances in thermoregulation, which may be paroxysmal or chronic and are commonly associated with disturbances in the sleep-wake cycle and food intake. Neurologic catastrophes, such as head trauma and subarachnoid hemorrhage, may manifest with paroxysmal sympathetic hyperactivity (hypertension, tachycardia, pallor, excessive sweating, hypothermia or hyperthermia) due to activation or disinhibition of hypothalamic and medullary sympathoexcitatory regions, including the PVN and rostral VLM. Medullary lesions, such as tumors, strokes, or syringobulbia, may manifest with paroxysmal hypertension, orthostatic hypotension, cardiovagal failure, or sleep apnea. High spinal cord lesions interrupting descending inputs to the preganglionic neurons may manifest with orthostatic hypotension and thermoregulatory failure as well as with paroxysmal unpatterned reflex sympathetic activity triggered by bladder distension and other stimuli (autonomic dysreflexia). Neurodegenerative disorders, such as multiple system atrophy, produce sympathetic and parasympathetic failure due to loss of preganglionic sympathetic and parasympathetic neurons, as well as neuronal loss in the VLM, medullary raphe, and other central autonomic nuclei.

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Central Sensitization

Definition

Increased sensitivity of central neurons processing sensory information.

►Hyperalgesia and Allodynia
►Pain

Central Set

Definition

The cognitive and emotional state of the individual, as it pertains to modulating effects on sensorimotor systems.

Central set is largely determined by prior experience and current expectations and is influenced by factors

such as affect (e.g. fear, anxiety, depression), arousal and attention.

►Anticipatory Postural Responses

Central Sulcus

Definition

The central sulcus (or fissure) separates the primary motor (precentral gyrus) and primary somatosensory (postcentral gyrus) areas of the cerebral cortex. It marks the boundary between the frontal and parietal lobes.

Central Tegmental Tract

Synonyms

Tractus tegmentalis centralis; Central tegmental tract

Definition

The central tegmental tract also known as the large longitudinal catecholaminergic bundles, is the most important terminal segment of the extrapyramidal-motor system. Uniting here are efferents from the corpus striatum, globus pallidus, red nucleus, reticular formation, central gray matter of ►Mesencephalon, pons and myelencephalon. The fibers chiefly terminate in the nucleus of the inferior olive from which a powerful tract passes to the cerebellum (olivocerebellar tract). In this manner, a motor feedback system is created, governing coordination of motor control.

►Pathways

Central Vestibular Disorders

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Synonyms

CNS vestibular disorders; Brainstem–cerebellar vestibular disorders; Non-peripheral vestibular disorders

Definition

Dysfunction of the vestibular system due lesions in the central nervous system (CNS).

Characteristics

Background

The vestibular system is divided into a peripheral portion, housed in the labyrinth of the inner ear, the vestibular portion of the ►VIII (= acoustic-vestibular) cranial nerve, and the central connections of the vestibular nerve. Clinically, disorders of the vestibular system are divided into peripheral (labyrinth) and central (CNS) [1]. Ear specialists (usually ear, nose and throat surgeons) may consider disorders of the VIII nerve as central but ►neurologists regard them either as peripheral or extra-axial (outside the neural axis).

Central vestibular disorders can be classified in different ways, according to (i) the underlying pathological process (e.g., inflammatory, demyelinating, tumoural, vascular, ►degenerative, traumatic), (ii) topography (e.g., medullary, cerebellar, cortical) and (iii) system involved (e.g., vestibulo-spinal, vestibulo-autonomic, vestibulo-ocular, vestibulo-cortical). Whenever possible, a physician would apply all these classifications simultaneously to his/her patient; for instance a patient can have a *degenerative* disorder of the *cerebellum*, predominantly involving the *vestibulo-ocular system*, as in the down-beat nystagmus syndrome (see below).

Vestibular Symptoms

In clinical practice it is customary to divide patients' problems into *symptoms*, what the patient reports (e.g., dizziness) and *signs*, what the examining doctor finds (e.g., nystagmus). The main symptoms in patients with vestibular disorders are vertigo, dizziness, oscillopsia and unsteadiness.

Vertigo is an illusion of body movement. The more common form is rotational or "true" vertigo in which patients feel that they are spinning round. Patients can also report that they see the world spin around them. Rotational vertigo is a useful symptom for diagnosis as it indicates involvement of the semicircular canals or their central projections. Apart from the canals and will nerve (as in peripheral vestibular disorders) the more frequent lesion site inducing vertigo is the area of the vestibular nuclei in the floor of the IV ventricle in the pontomedullary junction. More rarely patients describe sensations of linear bodily motion, called linear vertigo and thought to reflect involvement of the otolith organs or their central pathways.

Dizziness is more difficult to define. Patients with central vestibular disorders often use terms such as light-headedness, giddiness, dizziness or rocking sensations to describe their symptoms. Although common, these symptoms are less specific than vertigo for

indicating vestibular system disease as many general medical conditions (anemia, hypoglycaemia, arterial hypotension, psychological disorders) also provoke dizziness [1].

Oscillopsia is the illusion of movement or oscillation of the visual world. It is due to loss of stability of the visual image on the retina. Oscillopsia results from basically two situations, either the vestibulo-ocular reflex (VOR) is significantly reduced and as a result ocular stability during head movements is lost or the eye has involuntary movements such as nystagmus [2]. Bilateral peripheral disorders are usually responsible for the former whereas central disorders are usually the cause in the latter.

Unsteadiness. This is the result of direct disturbance in the vestibulo-spinal projection or functionally related structures, such as the vestibulo-cerebellum (the flocculo-nodular lobe). If the lesion is unilateral and acute, patients tend to fall to one side (lateropulsion), usually ipsilesionally as in lateral medullary stroke involving the vestibular nuclei (Wallenberg syndrome). If the lesion is bilateral or diffuse, as in progressive cerebellar degenerative disease, the patient is globally unsteady. It is important to realize that most central vestibular disorders are not confined to vestibular pathways and thus the unsteadiness observed in any individual patient is likely to result from involvement of other balance mechanisms, e.g., motor, cerebellar and proprioceptive pathways.

Vestibular Signs

The clinical findings that allow a distinction between a peripheral and a central vestibular disorder to be made are emphasized here. Apart from the presence of abnormal findings on the general neurological examination, such as limb weakness, anesthesia or ataxia, most signs indicative of a central vestibular disorder concern eye movement abnormalities. These include various forms of nystagmus, briefly mentioned below, as well as abnormalities in smooth pursuit, vestibulo-ocular reflex suppression and saccades, not discussed here.

Central Nystagmus

Nystagmus is an involuntary, repetitive back and forth movement of the eyes. During head or whole body rotation there is a normal physiological nystagmus, which consists of a slow velocity component stabilizing the eyes on earth-stationary objects and a fast phase that resets the eyes approximately to the middle of the orbit. Pathological peripheral vestibular nystagmus arises when a labyrinth on one side is hypoactive (or less frequently hyperactive). The slow phase is toward the damaged (hypoactive) side and the fast phase beats away from the lesion. Physiological and pathological nystagmus is labeled on the basis of the beat direction of the fast phase, e.g., destruction of the left labyrinth induces right-beating nystagmus.

The term central nystagmus indicates that the lesion is in the CNS. However, some forms of central nystagmus relate to non-vestibular ocular stabilization mechanisms (e.g., ►gaze paretic nystagmus, ►pendular nystagmus). In contrast, central vestibular nystagmus is specifically due to asymmetry in vestibular mechanisms controlling ocular stability; some examples are downbeat nystagmus (due to cerebellar floccular damage), spontaneous torsional nystagmus (due to unilateral vestibular nuclei lesions) and upbeat nystagmus (due to lesions interfering with the central vestibulo-ocular integrator in the ponto-medullary and ponto-mesencephalic tegmentum).

Main Central Vestibular Syndromes

The Downbeat Nystagmus Syndrome (DBNS) (or Vestibulo-Cerebellar Syndrome)

The main causes of the DBNS syndrome are (i) ►congenital malformation of the cranio-cervical junction (the Arnold–Chiari malformation), in which the cerebellar tonsils descend (herniate) into the spinal canal (hence the alternative name of "cerebellar ectopia"); (ii) cerebellar degenerations, sporadic or inherited; (iii) cerebellar disorders of various etiology, such as stroke, ►multiple sclerosis, neuro-toxicity and (iv) unknown, i.e., ►idiopathic. The lesion site frequently responsible for DBNS is the flocculo-nodular lobe of the cerebellum, also known as the vestibular cerebellum or archi ("ancient")-cerebellum, whose main afferent input comprises vestibular nuclear neurons. Patients with this syndrome complain of two main symptoms, unsteadiness of gait and vertical oscillopsia. The exact mechanism of the unsteadiness is not known but lesions of the flocculo-nodular lobe disrupt cerebellar processing of the vestibular input and, hence, gait ataxia develops.

Vertical opsillopsia is a reflection of the cardinal sign, downbeat nystagmus. The DBN is due to the fact that the pathways conveying the head-up vestibulo-ocular reflex traverse through the flocculus, hence lesions here create an imbalance in favor of the head-down VOR.

The flocculo-nodular lobe of the cerebellum also plays an important role in other ocular-motor functions, such as eccentric gaze holding, smooth pursuit and VOR suppression control. Accordingly, many patients also display abnormal gaze holding, in the form of gaze paretic nystagmus and abnormal pursuit and VOR suppression on clinical or laboratory examination of the eye movements.

Central Positional Nystagmus

An important step in the examination of the patient with balance or vestibular symptoms is the positional maneuver. The Hallpike or Dix–Hallpike maneuver is the most frequently used. The patient is rapidly moved by the examiner from the sitting position to a supine, ear-down position. The most frequent abnormality

found is due to a peripheral vestibular disorder called benign paroxysmal position vertigo (BPPV; see under peripheral vestibular disorders). In most disorders of the brainstem and the cerebellum involving central vestibular connections, a positional nystagmus is also induced. Since the physician does not normally know a priori whether the patient has a peripheral or a central vestibular lesion, careful examination of the positionally induced nystagmus is vital to establish a topographic diagnosis. Usually, peripheral positional nystagmus as in BPPV is accompanied by intense rotational vertigo ("positional vertigo") and discomfort, but these symptoms are less common and intense in central lesions. The more important distinctive features however, relate to the characteristics of the positionally induced nystagmus. In peripheral positional nystagmus there is usually a latency of several seconds to nystagmus onset after reaching the ear down position. The nystagmus subsides and disappears after 10–20 s ("adaptation") and diminishes on repeated positional maneuvers ("fatigability"). All these features, which are due to the underlying mechanism of canal lithiasis (canalolithiasis, see under peripheral vestibular disorders), are absent in central positional nystagmus. There is no latency so the nystagmus appears immediately on arrival in the ear down position and the nystagmus can persist for as long as the offending head position is maintained and reoccurs on each new positional maneuver (lack of adaptation and fatigability). Of utmost importance, the beat direction of the nystagmus in BPPV can be traced to a specific semicircular canal (usually the posterior canal) whereas this is usually not the case in central positional nystagmus. In particular, positional downbeat or upbeat nystagmus should raise a "red flag" for an underlying neurological condition.

Vascular Central Vestibular Syndromes

Vascular diseases of the CNS are divided into *ischemic* (loss of blood supply, usually due to atherosclerosis and thrombo-embolic phenomena) and *hemorrhagic* (bleeds). Bleeds into the subarachnoid space (subarachnoid hemorrhage) are usually secondary to ruptured aneurisms or arterio-venous malformations. Bleeds within the brain parenchyma are often secondary to hypertensive/atherosclerotic disease and less frequently due to aneurisms or arterio-venous malformations. In the acute stage, the clinical picture of a posterior fossa bleed is usually dominated by severe headache and potentially fatal alterations of consciousness, respiratory and autonomic function and neurological brainstem signs. The latter often include central ocular-motor and vestibular disorders, which if the patient survives can cause troublesome dizziness, unsteadiness, diplopia and oscillopsia secondary to a central vestibular syndrome.

The two main ischemic syndromes with central vestibular implications are infarctions in the territory of the posterior inferior cerebellar artery (PICA) and the anterior inferior cerebellar artery (AICA). The *PICA syndrome* gives rise to the lateral medullary or Wallenberg syndrome. In addition to infarction to the vestibular nuclei, various cranial nerve, sensory, motor and cerebellar pathways are involved (not reviewed here). Infarction of the vestibular nucleus produces a mostly torsional nystagmus (i.e., the eyes rotate around the line of sight, sometimes called "rotatory nystagmus") with the fast phase beating to the opposite direction of the lesion. An "ocular tilt reaction" can also be observed, in which the ipsilesional eye is lowered and the contralesional eye elevated, causing vertical diplopia (double vision) and an apparent tilt of visual scenes. These ocular vertico-torsional disorders are secondary to interruption of otolithic and vertical semicircular canal pathways to the eye muscles. The head can also be ipsilesionally tilted, due to lesion of the vestibulo-spinal (vestibulo-collic) projection.

Since the AICA irrigates not only brainstem and cerebellar structures but also the labyrinth itself, *infarctions of the AICA* cause a clinical picture combining central and labyrinthine features, including severe ipsilesional deafness.

Migraine

Although the most notorious symptom in migraine is headache, visual, auditory, somatosensory and vestibular features are also prominent. Although migraine is an inherited disorder, its symptoms are mostly episodic. Triggers for the episodes can often be identified and include sleep deprivation, certain foods (e.g., red wine, chocolate) and intense sensory stimulation such as bright lights. The underlying biochemical disorder responsible for migraines is not fully understood, but vascular mechanisms, channelopathies (dysfunctional neuronal membrane ion channels) and peptide-mediated irritation of V nerve terminals may all play a part.

Migraneous headaches are pulsating or "throbbing," accompanied by nausea and intolerance to loud sounds (phonophobia), bright lights (photophobia) or smells (osmophobia). In recent years, the role of migraine as one of the main causes of episodic vertigo has been recognized. In parallel it has been observed that vestibular stimulation and motion sickness can trigger migraine in susceptible subjects. Observations of migraine patients in the middle of their vertiginous attacks indicate that peripheral (labyrinthine) and central vestibular syndromes or both can occur [3]. The treatment of vestibular migraine is not standardized as there are no good randomized control trials published, but most clinicians believe that preventive (prophylactic) treatment with beta-blockers such as

propranolol is moderately effective. The International Headache Society (IHS) periodically reviews the classification of migraine and headaches, although vestibular issues do not feature prominently in their discussions.

Disorders of the Vestibular Nerve

The most frequent disorder of the vestibular nerve is a slowly growing benign tumor called *vestibular schwannoma or acoustic neuroma*. The most prominent symptom caused by this tumor is due to compression of the acoustic rather than the vestibular portion of the VIII cranial nerve, since patients report slowly progressive unilateral deafness and tinnitus. Although the vestibular nerve is equally damaged by the neuroma, its slow progression rarely leads to noticeable unsteadiness or vertigo. As the tumor grows it eventually leads to compression of other structures in the cerebello-pontine angle, including the V, VI and VII cranial nerves and the cerebellar flocculus. This level of growth is exceptional these days, as the diagnosis is established earlier with neuro-radiological procedures, in particular MRI scans.

Neurofibromatosis 2 (NF2) is an autosomal dominant disease characterized by the development of nervous system tumors, ocular abnormalities and skin tumors. Vestibular schwannomas (usually bilateral) occur in about 95% of adult NF2 patients and presenting symptoms are audio-vestibular. In contrast, children with NF2 often present with non-VIII nerve tumors and non audio-vestibular symptoms [4]. Other forms of neurofibromatosis are not dealt with here.

Diagnostic Procedures in Central Vestibular Disorders

A reliable clinical history provides vital clues as to whether symptoms of vertigo, dizziness, oscillopsia or unsteadiness are caused by peripheral or central vestibular disease. In favor of a central topography are symptoms attributable to brainstem and cerebellar structures, such as numbness (V) or weakness (VII) of the face, speech disturbance (cerebellar ►dysarthria), swallowing difficulties (IX, X) or to long tracts, such as unilateral body weakness or numbness. Although unilateral hearing symptoms can occasionally be due to central disease (e.g., see AICA syndrome above) they are more common in peripheral (e.g., Meniere's disease) or VIII nerve (e.g., vestibular schwannoma) disease.

In the clinical examination, the physician seeks to establish if there are abnormalities attributable to CNS disease, e.g., abnormalities of the motor-sensory systems such as hemiparesis, hemianesthesia or ataxia. The presence of signs of cranial nerve dysfunction (e.g., facial weakness or anesthesia), central nystagmus (torsional, pendular, gaze paretic, central positional nystagmus) and other abnormalities of eye movements, such as slow or ►dysmetric saccades and broken up pursuit or VOR suppression, are particularly important.

Electro-oculography, EOG, (or electro-nystagmography, ENG) and video-oculography, VOG are eye movement recording techniques which allow laboratory examination of vestibular and eye movement functions in a standardized and quantitative manner. Visuo-motor function is assessed with illuminated visual targets for gaze holding, smooth pursuit and saccades. Vestibular stimulation is delivered either with physiological stimuli, such as rotational techniques or with the caloric test. These tests are normally carried out in darkness to avoid confounding visuo-motor effects. The caloric test consists of individual irrigation of the external auditory canals with water or air that is cooler (30°C) or warmer (44°C) than body temperature. This creates a transient asymmetry in vestibular function, mostly in the horizontal semicircular canal system, in turn inducing nystagmus that can be recorded and quantified.

In unilateral or bilateral peripheral vestibular disease the main abnormality is a reduction in rotational or caloric responsiveness, uni- or bi-laterally respectively. In contrast, in central vestibular disorders the main indicator of CNS disease is the presence of abnormal pursuit, VOR suppression or saccades, even if vestibular symmetry to caloric or rotational stimulation is preserved. Examination of the waveform of a spontaneous or gaze evoked nystagmus can also help to distinguish between peripheral and central vestibular disease and between acquired and congenital nystagmus.

Neuro-imaging constitutes the major step in identifying (or ruling out) the presence of a structural intracranial abnormality. Current imaging techniques do not have sufficient resolution to detect abnormalities in the in vivo labyrinth in the vast majority of peripheral disorders (except some congenital abnormalities or in the superior semicircular canal dehiscence syndrome). In contrast, the majority of diseases giving rise to central vestibular syndromes can be visualized, e.g., degenerative (atrophic) cerebellar–brainstem disorders, demyelination including multiple sclerosis, spontaneous or traumatic hemorrhage as well as ischemia, tumors and cranio-cervical disorders. In general, MRI is superior to CT scan for disorders of the cerebellum, brainstem and the VIII and other cranial nerves.

General *blood tests* are of only limited function in the evaluation of a patient with central vestibular symptoms. They are however useful to rule out that patients' symptoms are not provoked by a general medical condition such as anaemia or inflammatory/infectious disorders. *Neurogenetic testing* can be useful particularly

in cases where a positive family history of neurological disorder is present, as in inherited cerebellar disease [5] and NF2. The list of familial disorders identified genetically is growing fast and neurogenetic testing is widespread nowadays; hence neurogenetic testing is often carried out in patients despite the absence of a known family history.

Physiological (Non-Structural) Vestibular Disorders (Mismatch; Motion Sickness; Visual Vertigo)

Motion Sickness ("Car Sickness"; "Sea Sickness")

Motion sickness is a common experience at some point in our lives. Symptoms of nausea, pallor, cold sweatiness and vomiting can be induced by land, air or sea travel in most normal subjects. However, susceptibility varies greatly within the population and within an individual, with children and women being more susceptible than adult males. A possible hormonal influence underlying this trend is suspected. Apart from its impact in the general population, motion sickness is intensively studied because of its impact in civilian and military air and sea crews [6].

Mechanisms

The vestibular system plays a prominent role in motion sickness as indicated by the fact that subjects lacking vestibular function cannot be made sick by motion. Also, the autonomic symptoms induced by caloric and rotational stimulation of the labyrinth or by vestibular disease are almost identical to those of motion sickness. Motion dynamic characteristics are important; low frequencies particularly centered at 0.10–0.30 Hz (e.g., one cycle every five seconds) as experienced on ships are more provocative than faster frequencies as experienced in a small sports car.

Visual field motion (= optokinetic stimuli) can also induce similar but less intense sickness. This is explained by the fact that optokinetic stimuli activate central vestibular neurons and induce sensations of self-motion (= vection). An example of a vection illusion is that induced by departure of a train on the track next to the train on which one is seated.

There is no ecological explanation as to why animals and humans should develop motion sickness. Neural projections between the vestibular system and the autonomic centers (including vomiting centers) in the floor of the IV ventricle underlie the gastric and circulatory physiological phenomena. A possible role of the vestibular system in detecting circulating toxins, where vomiting would have a beneficial role in precluding further intestinal absorption, has been discussed; alcohol intoxication is an example. Also, the fact that motion sickness is more readily induced in situations of sensory conflict (= disorientation mismatch; see below) suggest that the unpleasant sensations induced may serve the purpose of raising awareness that conditions in the environment are unusual and potentially threatening for the organism. For instance, the motion sickness symptoms experienced when locked up in a moving enclosure, as inside a ship with no windows, are partly due to the visuo-vestibular conflict in which vestibular cues inform the CNS that there is body motion but visual cues do not confirm it. If the person finds the way to the deck and looks at the moving horizon, the sensory conflict is resolved and motion sickness improves to some extent.

Treatment

Prevention is the best tactic against motion sickness. Drugs used to prevent motion sickness belong to two main groups, anti-muscarinic (scopolamine = hyoscine) and antihistaminic (cinnarizine; cyclizine), which are used for their central (CNS) effects on vestibular and vomiting centers. Scopolamine is considered to be the most effective drug. Non-pharmacological treatment is effective and consists of de-sensitizing the subject to the provoking stimuli, namely body and visual motion. The motion devices required for this treatment are relatively complex and the treatment is usually reserved for professional air and sea crews.

Mismatch Disorientation (Visuo-Vestibular Conflict)

This is the name given to the spatial disorientation, dizziness and motion sickness that arise when a subject is exposed to conflicting sensory information.

Orientation in space is provided by various sensory channels, of which the more important are the visual, vestibular and proprioceptive systems. In normal circumstances the information provided by these various inputs is coherent and congruent. For instance, when we turn our heads the motion provided by these systems agrees with each other. Two common examples in which sensory conflict arise are (i) being inside a ship or reading while riding a bus, where vestibular input signals head motion but visual input does not (because the visual scene remains head-fixed and the eye sees no change with respect to the visual surroundings) and (ii) when viewing tilted or moving large visual scenes. In the latter case the visual input is centrally interpreted as due to self-motion, but this is not confirmed by the vestibular or proprioceptive systems.

As with motion sickness, the susceptibility to becoming disoriented or dizzy due to conflicting visuo-vestibular input varies greatly within the population. One of the factors involved in this variability relates to how much "weight" an individual places on his/her visual input for spatial orientation. This is so because vision, as a non-inertial sensory system, is more likely to provide the "wrong" information when sensory conflict arises. Hence, subjects who place more weight on vision ("visually dependent") are more likely to

experience disorientation than those who rely more on inertial cues for spatial orientation.

Visual Vertigo (= Space and Motion Discomfort; Visuo-vestibular Mismatch)

This is a syndrome that develops in some patients with peripheral vestibular disorders, although it is based on central physiological mechanisms akin to "mismatch disorientation" (see previous paragraph).

In the majority of patients with acute peripheral vestibular disorders the central process of vestibular compensation suppresses the symptoms (e.g., dizziness) and signs (e.g., nystagmus; postural imbalance) within weeks or a few months. In some patients, symptoms continue ►chronically, particularly when visuo-vestibular conflict arises, such as viewing moving visual scenes as in traffic or in complex urban scenarios such as supermarkets. Research has shown that increased visual dependence (see previous paragraph) underlies the syndrome of visual vertigo [7]. Desensitization techniques such as those used for motion sickness, with special emphasis on visual motion stimuli are helpful aids in the rehabilitation of these patients [8].

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Central Vestibular Lesions

Definition

►Central Vestibular Disorders

Centrifugal Fibers in Olfactory System

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C

Synonyms

Central projections; Centrifugal inputs

Definition

The olfactory system is at the interface of the environment and the central nervous system. It is responsible for coding sensory information from thousands of odorous stimuli. To accomplish this, odor information must be processed through various levels. A modified representation of the odor stimulus is generated at each level. In mammals, an olfactory stimulus activates an ensemble of olfactory receptor neurons in the olfactory epithelium, each of which expresses an odorant receptor. These sensory neurons project to the first central relay of the olfactory system, called the main olfactory bulb, where the olfactory nerve contacts the bulbar output neurons, the mitral and tufted cells. These neurons project directly to the olfactory cortex. The olfactory bulb is the first major site of integration for olfactory information.

The olfactory bulb does more than processing sensory information; it also integrates information communicated via centrifugal projections (fibers) from many central structures [1]. Olfactory perception is strongly influenced by experience. Thus, these centrifugal fibers may modulate the function of olfactory microcircuits at various sites in a concerted fashion to tune olfactory bulb processing. This centrifugal modulation may influence the meanings associated with particular odorant perceptions, depending on the internal state or experience of the animal. It may also play an important role in attentional processes, as is the case for other sensory systems.

Characteristics

There are many types of centrifugal fibers projecting to the olfactory bulb from various brain areas [1]. We can mainly distinguish glutamatergic feedback projections from the olfactory cortex and fibers coming from modulatory structures, e.g., the raphe, the locus coeruleus, and the basal telencephalon.

Feedback Projections from Olfactory Cortical Structures

Glutamatergic afferences are coming from many brain areas including several cortical regions and some hippocampal structures. The feedback projections coming from olfactory cortex are the main centrifugal fibers

innervating the olfactory bulb (Fig. 1). They project mainly onto somata or basal dendrites of granule cells, the main GABAergic interneurons of the olfactory bulb [1].

It has been shown earlier that stimulation of primary olfactory cortical structures or anterior commissure, which is the major route for centrifugal fibers, produces a negative ►local field potential (LFP) in the granule cell layer (GCL) consistent with an activation of granule cells. More recently, ►patch clamp recording has confirmed that stimulating the piriform cortex produces excitatory postsynaptic currents (EPSCs) (►Postsynaptic currents (EPSCs and IPSCs) or potentials (EPSPs and IPSPs)) in granule cells [2].

The main role of granular GABAergic interneurons is to deliver inhibitors onto mitral cell dendrites via reciprocal dendrodendritic synapses. These synapses allow recurrent release of inhibitors onto activated mitral cells and lateral inhibition between two neighboring mitral cells. These phenomena are thought to be the basis of mitral cell synchronization, ►network oscillations, and contrasted responses to various odorants. Modulating granule cell responsiveness to mitral cell stimulation may be a very efficient way to modulate olfactory bulb activity in response to odorant activation.

Many studies demonstrate that dendrodendritic inhibition of mitral cells depends on activation of granule cell spines via AMPA and NMDA ionotropic glutamate receptors. However, NMDA channels are tonically blocked by extracellular Mg^{2+}. Repetitive stimulation of terminals arriving in the GCL or tetanic stimulation in the piriform cortex produces a large depolarization of granule cells sufficient to remove the Mg^{2+} blockade of NMDA receptors in the granule cell spines [2]. This mechanism allows efficient triggering of GABA release by activation of the reciprocal synapse.

The ability of granule cells to inhibit mitral cells is highly dependant on their excitation by centrifugal inputs. Thus, any changes in the characteristics of these excitatory inputs may have large consequences on the properties of the entire network. Controlling granule cell inhibition of mitral cells is a powerful way for the cortex to modulate olfactory bulb activity.

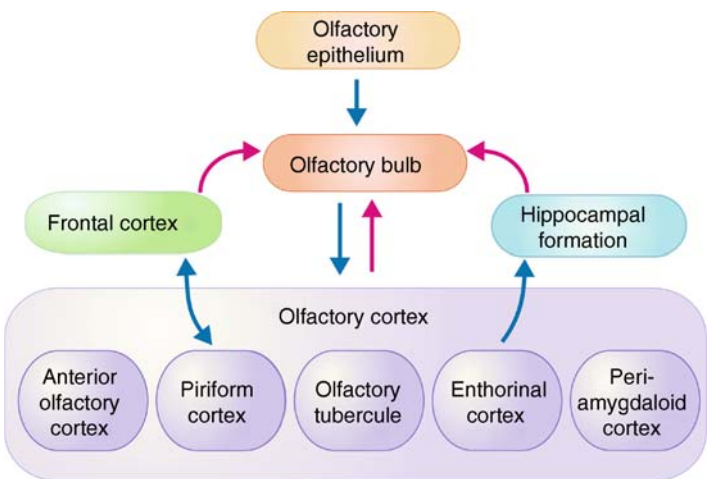
For example, it is known that beta frequency oscillations of the olfactory bulb network are essential for olfactory function and can be modified by olfactory experience. They are enhanced during olfactory learning tasks and repetitive presentation of an odorant. Disruption of cortical centrifugal fibers eliminates odor-evoked ►beta oscillations and their experience-dependant enhancement. The integrity of these cortical projections is also essential for the formation of odor-reward olfactory associations [3].

Neuromodulatory Projections

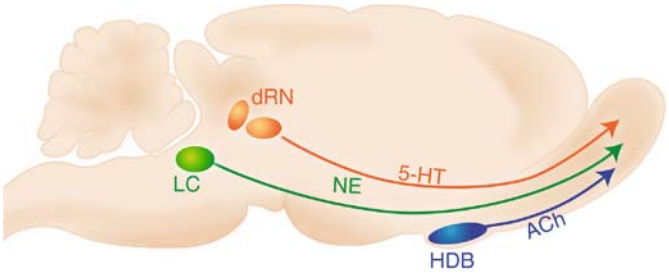
In addition to the massive innervation by glutamatergic terminals, the olfactory bulb receives inputs from neuromodulatory regions (Fig. 2). Cholinergic, noradrenegic, and serotoninergic fibers reach the olfactory bulb circuit to modulate the network activity at several synaptic and extrasynaptic levels.

Cholinergic fibers extend from the horizontal limb of the diagonal band of broca (HDB) to every bulbar layer, but their principal target is the dendrodendritic synapse between the granule cells and the mitral cells in the external plexiform layers [1].

Acetylcholine has various effects, depending on cell type. This ►neuromodulator increases the excitability



Centrifugal Fibers in Olfactory System. Figure 1 Main glutamatergic projections onto olfactory bulb. The olfactory bulb receives feedback projections from every part of the olfactory cortex. It also receives glutamatergic projections from other cortical areas (including frontal cortex) and from hippocampal structures.



Centrifugal Fibers in Olfactory System. Figure 2 Neuromodulatory projections onto olfactory bulb. Neurons from the horizontal limb of the diagonal band of broca (HDB) are releasing acetylcholine (Ach). Neurons from the dorsal raphe nucleus (DRN) are releasing serotonine (5-HT). Neurons from the locus coeruleus (LC) are releasing norepinephrine (NE).

of periglomerular interneurons and mitral cells via the synaptic and extrasynaptic nicotinic receptor [4]. Conversely, acetylcholine acts on the soma of granule cells via the muscarinic receptor to decrease their excitability and acts on their dendrites to increase the release of GABA.

These cholinergic fibers are beginning to be recognized as being heavily involved in olfactory function. Spontaneous olfactory discrimination is impaired when these fibers are damaged and is more accurate with increased efficiency of these fibers. if the nicotinic receptor is blocked in the olfactory bulb, the animal cannot discriminate between two closely related odorants [5].

Noradrenergic fibers extend from the locus coeruleus. In vivo studies of behaving animals have shown that olfactory cues increase the activity of locus coeruleus noradrenergic neurons and lead to an increase in norepinephrin concentration in the olfactory bulb. The spatial distribution of these fibers is highly specific. They innervate mainly the inner plexiform layer (IPL) and the GCL. Only a few fibers penetrate the external plexiform layer (EPL); however, the main targets of these ▶neuromodulators are the dendrodendritic synapses between mitral cells and granule cells. Norepinephrin impairs the release of GABA from granule cell dendrites. It also decreases spontaneous synaptic activity in mitral cells and granule cells.

The influence of norepinephrine on olfactory performance depends on the age of the animals. In neonates, within the first postnatal week, the locus coeruleus is essential for formation and stabilization of conditioned olfactory learning [6]. In adults, norepinephrin is involved in the consolidation of olfactory memory.

Serotoninergic fibers extend from the dorsal raphe nuclei and innervate the glomeruli. In neonate rats, serotoninergic activity is important for conditioned learning [6]. Intrabulbar infusion of serotoninergic antagonists prevents formation of olfactory preference. In adult rats, the injection of a serotoninergic neurotoxin impairs olfactory discrimination [7].

Centrifugal Inputs and Network Plasticity

Centrifugal projections extending from olfactory and neuromodulatory structures act together to regulate activity of the main olfactory bulb. This concerted modulation of olfactory information processing illustrates the intensive crosstalk between these areas of the brain.

The large variety of centrifugal projections and cell types innervated by these fibers give this system a high level and various sources of plasticity. There are many situations in which the olfactory bulb needs to be highly plastic. Behavioral studies clearly demonstrate the major role of centrifugal projections in enhancement of spontaneous odor discrimination, olfactory learning, and recall of specific olfactory memories. Furthermore, computational modeling has suggested that these inputs may increase in contrast in mitral cell responses to various odorants.

Physiological studies have shown the possibilities of long lasting changes in the strength of centrifugal inputs and the excitability of olfactory bulb neurons. Centrifugal fiber's stimulation in fish can induce long-term potentiation (LTP) at the mitral cell to granule cell synapse [8]. Additionally, in vivo recordings in anesthetized rats have shown that high-frequency stimulation in the GCL can induce LTP of centrifugal inputs to granule cells [9].

Another major source of plasticity in the olfactory bulb network is continuous neurogenesis in the adult, consisting of production of granular and periglomerular interneurons throughout the life of the animal. As interneurons are the main targets of centrifugal projections and as adult neurogenesis is regulated by olfactory experience and sensory activity [10], this extreme form of network plasticity may be controlled by the concerted action of neuromodulators and feedback excitatory projections.

Centrifugal Inputs and Attention

Feedback projections from cortical structures play a major role in attentional processes in other sensory

pathways, including the visual system. The existence of attentional mechanisms in the olfactory system is under debate; presence of the classic type of attentional processes, as in other sensory systems, is excluded by the fact that the olfactory centrifugal projections do not pass through the thalamus. However, some of the defects in olfactory performances reported in behavioral studies of animals with altered centrifugal innervation may be interpreted as an impairment of olfactory attention.

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Centromedian Nucleus

Synonyms

Nucl. Centromedianus; Centromedian nucleus

Definition

The centromedian nucleus belongs to the Intralaminar thalamic nuclei and receives its afferents from motor and parietal cortex as well as from the globus pallidus. It projects to the putamen, which in turn projects to the globus pallidus. This functional loop conveys poly-sensory information to the corpus striatum, which is important for execution of correctly oriented motor responses.

►Diencephalon
►Headache

Cephalagia

►Headache

Cerebellar Commissure

Synonyms

Commissura cerebelli; Cerebellar commissure

Definition

The two cerebellar hemispheres communicate via long commissural fibers. The associated bundle of fibers crossed the vermis cerebelli close to the fastigial nucleus. The preceding part is called the anterior cerebellar commissure and the succeeding part is known as the posterior cerebellar commissure (Stilling).

►Cerebellum

Cerebellar Cortex

Synonyms

Cortex cerebelli; Cerebellar cortex

Definition

Just like the cerebrum, the cerebellum also evidences a pronounced cortical structure. The gray nuclear cortex is greatly folded and interspersed with white, fiber-containing matter. The cerebellar cortex has a typical cyto-architecture whose chief components are Purkinje cells, granular cells, basket cells and Golgi cells.

The cerebellar cortex compares motor program with motor action and optimizes the motor program.

►Cerebellum

Cerebellar Corticonuclear Projection

Definition

The topographical projection of Purkinje cells located within the sagittal zones of the cerebellar cortex to specific locations in the cerebellar nuclei.

►Cerebellar Functions
►Purkinje Cell, Neuron

Cerebellar Functions

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Definition

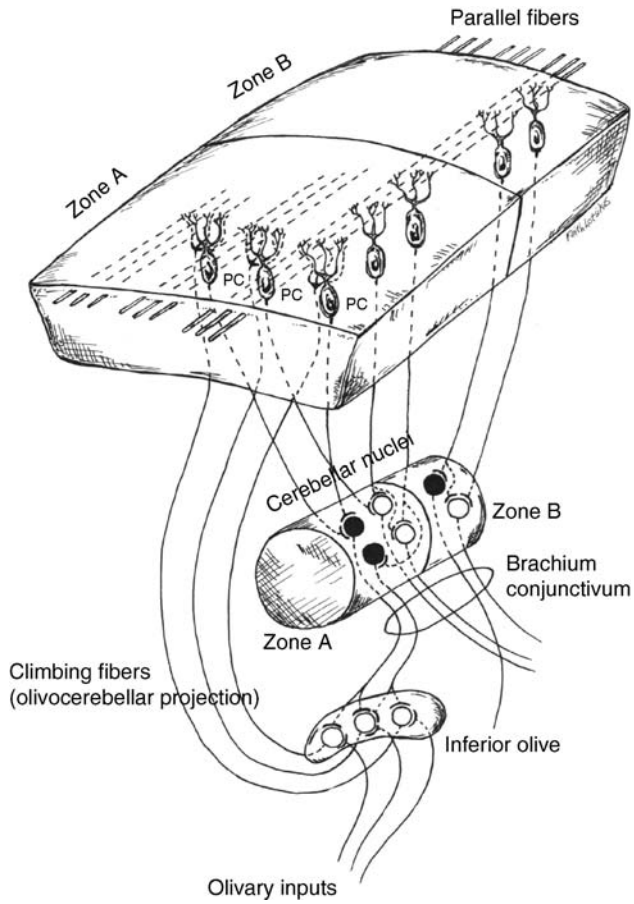
Defining the function of the cerebellum has been an elusive target of investigators for at least a century. Most initial inferences resulted from ablation experiments in animals and clinical studies of cerebellar patients. In general, disturbances in balance, posture, eye movements, and control of volitional, goal-directed movements were observed. Fundamentally, these disturbances were primarily related to the fine control of various movements, not an inability to initiate or execute the task. Based on these observations, the cerebellum was considered to play a major role in regulating a wide variety of motor behaviors with little involvement in nonmotor functions. This restrictive view changed dramatically in the early 1980s with the discovery that lesions of the cerebellum in otherwise intact animals made it impossible to acquire and recall the classically conditioned eyeblink reflex. More recent imaging studies showed correlates of neuronal activity in the cerebellum during a variety of cognitive tasks. Consequently, it is now well accepted that the cerebellum is engaged in motor as well as nonmotor functions.

Characteristics

Functional Organization of Cerebellar Systems

Structurally, the cerebellum consists of a foliated cortex and the deep cerebellar nuclei. The output neurons of the cerebellar cortex, the Purkinje cells, project to the cerebellar nuclei as the corticonuclear projection (►cerebellar corticonuclear projection), and the output neurons of the deep nuclei convey the information processed in the cerebellum to the brainstem and thalamus. The cortex and corresponding regions of the cerebellar nuclei are organized into ►sagittal zones. Traditionally, the cerebellum is divided into three primary sagittal zones: the midline (vermal), the intermediate (paravermal), and the lateral (hemispheric) zones. However, detailed neuroanatomical studies indicate that there are at least eight such zones in higher vertebrates, depending on the species and the region of the cerebellum. In general, these more restrictive zones specify the location of Purkinje cells within the cerebellar cortex projecting to a specific medio-lateral location in the deep cerebellar nuclei. In addition these zones define the topographic distribution of the climbing fiber projection (the olivocerebellar projection) originating from specific locations in the inferior olive. The relation of these zones to the olivocerebellar system will be discussed below. These relationships are characterized in Fig. 1.

The output of the cerebellum originates largely from the cerebellar nuclei, with the exception of some Purkinje cells that project from the vermal region to components of the vestibular system. These output pathways affect neuronal interactions in the spinal cord, numerous brainstem nuclei, as well as the hypothalamus, thalamus and cortex. The vermal, intermediate, and lateral cerebellar regions, the larger sagittal zones described above, are each related to a specific set of afferent and efferent projections. The midline or vermal zone, of which the fastigial nucleus is a part, interacts extensively with the vestibular system, components of the eye movement system, and descending projections to the spinal cord originating primarily from the medulla. These descending projections play an important role in the regulation of posture and locomotion. The intermediate zone and the associated interposed nuclei are unique in having extensive interconnections with the spinal cord as well as the pontine nuclei, the thalamus, and the cerebral cortex. This zone is involved in the coordination of ongoing volitional movements, and it also is involved in the regulation of spinal reflexes, including the ►cutaneomuscular reflexes. The lateral region, associated with the dentate nucleus, interacts primarily with the corticopontine and the thalamocortical projections, particularly those related to portions of the cortex involved in motor planning and other higher cortical functions. In addition to playing an important role in the performance of complex, goal-directed limb movements, it is primarily involved in regulating movements requiring the integration of motor behavior with higher cortical functions. Components of the hemispheres may also play a role in the control of eye



Cerebellar Functions. Figure 1 Diagrammatic illustration of the cerebellar-olivary loop, a set of interconnections relating the nuclear projection of Purkinje cells (PC) to the projection of climbing fibers from the inferior olive to the cerebellar cortex. Note the corresponding projections from Zones A and B to the related regions of the deep nuclei. Inhibitory nuclear neurons project in turn to olivary neurons which ultimately terminate on Purkinje cell dendrites in the same sagittal zones. Brachium conjunctivum: ascending output projection from the cerebellar nuclei. In the cerebellar nuclei and inferior olive, clear cells are excitatory and filled cells are inhibitory.

movements. (See [1] for additional information regarding the movements regulated by each zone.)

Across all of the zones, there are two primary types of afferent projections to the cerebellum, the mossy fibers and the climbing fibers. In general, each afferent pathway projects to both the cerebellar cortex and the nuclei, although the majority of projections are received by the cerebellar cortex. Mossy fiber projections originate from multiple sites within the brain and spinal cord receiving inputs from the same sagittal zone to which these afferents project. These include inputs from virtually all sensory modalities that are important for the control of movement, inputs from the collaterals of output neurons in the cerebellar nuclei, and from the cerebral cortex. Mossy fibers inputs projecting from different regions of the body terminate in a pattern within the cerebellar cortex called a "patchy mosaic." The representation of different body regions are intermixed in a mosaic-like distribution across the folia of specific cerebellar cortical regions. The inputs to the cerebellar cortex from mossy fibers are conveyed by a cerebellar cortical neuron, the granule cell, which in turn projects to the Purkinje cells via parallel fibers. These fibers are shown in Fig. 1 without their relation to their cells of origin, the granule cells. Mossy fiber projections are responsible for providing the graded modulation of Purkinje cells and nuclear cells that reflect the magnitude of relevant sensory inputs as well as the activity in descending motor pathways important for initiating and controlling movement.

Each of the approximately eight sagittal zones also receives a specific projection from a unique afferent system, the climbing fiber system. As shown diagrammatically in Fig. 1, the climbing fibers projecting to a specific sagittal zone originate from a region of the inferior olive receiving an inhibitory input from neurons

located in a corresponding zone of the cerebellar nuclei. The dendritic tree of a single Purkinje cell receives an input from only one climbing fiber, although each climbing fiber can branch and contact other Purkinje cells in the same zone. The contribution of these loops to the function of the cerebellum is in the early stages of investigation.

This unique afferent projection is activated under specific functional conditions and produces a very large depolarization of the Purkinje cell dendritic tree. These afferents are known to generate these responses following unexpected sensory stimuli as well as during certain features of a voluntary movement. In addition, they respond to vestibular inputs and moving visual stimuli (stimuli moving across the retina). See [2] for a brief review. The functional significance of the unique responses they evoke is still being discussed. Proposals include the induction of plastic changes in the responses of Purkinje cells, the generation of synchronous responses of cerebellar nuclear neurons, and the signaling of specific features of a sensory stimulus.

It is beyond the scope of this review to describe these systems further except to emphasize that they provide a substrate for integrating multiple sensory inputs with information characterizing the activity in descending projections involved in generating movements. The importance of the cerebellum in integrating a variety of sensory information with the control of ongoing movement is emphasized by the fact that this structure receives inputs activated by virtually all types of sensory stimuli. These inputs provide updated information about the movement and position of the extremities, balance, and multiple characteristics of the environment. Very importantly, cerebellar systems are designed to modify motor behavior as a consequence of integrating information from sensory pathways with information from the pathways more directly responsible for generating movements. The cerebellum's efferent projections are among the most diverse of the nervous system, making it feasible for the cerebellum to influence all aspects of motor behavior as well as autonomic and cognitive functions of the nervous system.

Regulation of Motor Behaviors

One of the primary functions of the cerebellum is the real-time control and coordination of a wide variety of movements. Characteristically, the more precise and complex the movement and the greater the integration required for its execution, the more the cerebellum is involved in its control. In general, the cerebellum is particularly important for the coordination of discrete, goal-directed smooth pursuit movements of the eyes (►smooth pursuit eye movements), control of ►gaze, and the regulation of multijoint movements of the extremities, particularly those requiring the integration of postural changes with phasic limb movements. This structure is also important for the coordination of combined eye and hand movements.

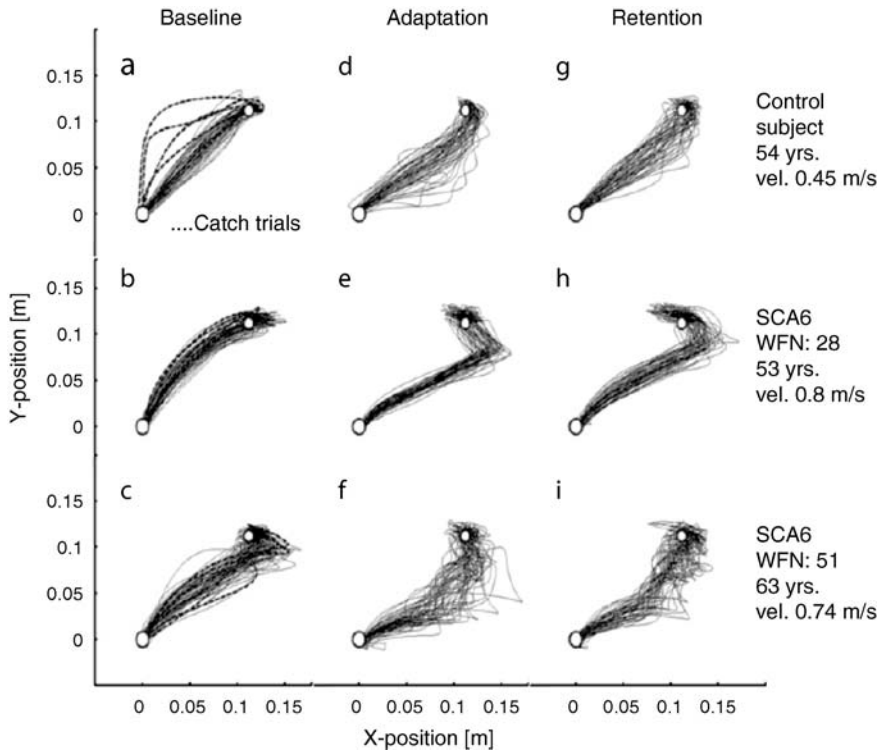
Cerebellar circuits utilize both feedforward and feedback control mechanisms in regulating these movements. However, much of the literature emphasizes the importance of the cerebellum in predictive or feedforward control mechanisms (See [3] for Review). In general, feedforward mechanisms are utilized to generate preparatory modifications in motor output that enhance the performance of previously rehearsed or experienced movements. Feedforward control involving the cerebellum is particularly important in establishing ►motor set and scaling of responses when novel tasks require modification of movements to attain a target accurately.

An example of this is shown in Fig. 2. In these experiments [4], cerebellar patients and normal controls were asked to move a manipulandum from a start position to a specific target through a force field, a velocity-dependent directional load imposed on the movement.

This force field deflected the movement down and to the right as the manipulandum moved from the start position to the target. It was necessary for a subject to properly predict the change in muscle activation required to compensate for the force field in order to move to the target in a straight line. Normal subjects (Control, top row) can acquire this capability after adequate practice. However, cerebellar patients who had spinocerebellar ataxia (SCA), even those that were not so ataxic (patient shown in B, E, and H) were incapable of compensating for the imposed force field. It is important to note that this type of cerebellar deficit appears task- and/or condition dependent. For example, animals with the critical components of the cerebellar efferent systems inactivated are still capable of acquiring and retaining compensation for a different type of elastic load applied every trial in a reaching task (see [5] for review of task dependency).

Likely related to the use of feedforward mechanisms is the capacity to establish ►internal representations critical to the performance of the task. These representations may relate to properties and location of the target, dimensions defining extrapersonal space, features of the musculoskeletal system and/or body image, and elements of the motor sequence. Experiments of the type illustrated in Fig. 2 suggest that cerebellar patients cannot form the appropriate internal representation of the force field. Other experiments indicate that this deficit is not limited to properties of the work space. For example, cerebellar patients also have deficits representing object shapes, particularly when the characteristics of the shapes must be acquired using kinesthetic cues.

In addition, the cerebellum also participates in feedback regulation by playing a role in modifying motor responses on the basis of updated information



Cerebellar Functions. Figure 2 Trajectories of a control subject and two cerebellar patients (WFN: 28 and WFN: 51) from a start position (*circle*, *lower left*) to a target (*circle*, *upper right*). A–C: control trials. Catch trials, trials in which no force field was applied during the trials in D–I, are shown as dashed lines. D–F: trials during adaptation. G–I: trials during the test for retention. Note that the force field consistently displaced the trajectory of the cerebellar patients. However, the control subject effectively compensated and also retained the task. Catch trials illustrate that the control subject had learned a new strategy to compensate for the load, since in the absence of the load, the movements demonstrated an after effect, a movement approximately opposite to the one learned in order to compensate for the load. *SCA*, spinocerebellar ataxia. Figure is from [4].

about the progress and accuracy of an ongoing movement. Consequently, this structure is very important in generating coordinated responses to perturbations encountered during the execution of a variety of tasks.

As introduced above, certain eye movements are among the movements most dependent upon the cerebellum for their normal performance. Without the required cerebellar circuitry, eye movements necessary for following slowly moving objects in the visual field, designated smooth pursuit movements, cannot be performed. In addition, very rapid or saccadic movements of the eyes are very dysmetric in the absence of cerebellar control. Finally, portions of the midline cerebellar region are critical for the full adaptation of the ►vestibular ocular reflex, a process required for recalibrating the movement of the eyes relative to the movement of the head.

Motor Learning and Higher Cortical Functions

Considerable evidence has implicated the cerebellum in the learning of a wide variety of motor behaviors. These range from classically conditioned reflexes to complex, operantly conditioned tasks. The specific contributions of the cerebellum to this function are reviewed in other entries in the Encyclopedia. Consequently, this overview will focus on the cerebellum's involvement in higher functions other than motor learning.

Studies implicating the cerebellum in other nonmotor functions have utilized imaging techniques such as fMRI and PET to illustrate changes in the activity of cerebellar regions during the execution of certain complex tasks, or they have examined the deficits manifested by cerebellar patients in related behaviors. Acknowledging that studies of this type provide strong inferences that the cerebellum is involved in these behaviors, they do not implicate this structure *causally* nor do they indicate *how* the cerebellum might be involved. That said, there is substantial evidence for the involvement of the cerebellum in the following higher order functions: solving tasks requiring the manipulation and perception of objects during the

solving of puzzles such as the Tower of Hanoi, certain word association and word selection tasks, perception of tone duration, the characteristics of imagined movements, and the perception of object shapes during ongoing movement. In addition, the occurrence of autism and schizophrenia has been associated with structural abnormalities in the cerebellum (See [6] for review).

Summary: Overview of Cerebellar Function

The above sections emphasize that the cerebellum receives information from virtually every sensory system as well as from projections originating from structures important in motor control. In addition, the cerebellum plays at least some role in most if not all aspects of motor behavior. This heterogeneity of involvement has made it very difficult to assign a single function to this interesting structure. In attempting to integrate this information, general hypotheses have been proposed suggesting that the cerebellum acts as a "mediator" or "metasystem" for integrating information from multiple sensory systems on-line with information characterizing the task and the state of the organism in order to generate an optimized, well-coordinated movement ([7–9], see also the "context linkage" proposal of Thach [6]). The sensory systems convey information about the external environment or the influence of the environment on the body, each with its own unique reference frame (See [10] for overview of reference frames). These data must be effectively integrated with data represented in internal reference frames reflecting features of the intended movement and body scheme as well as with reference frames describing muscle space and execution space. Although the cerebellum and its afferent and efferent projections appear to be appropriately organized to contribute to this complex function, little is known regarding precisely how this integration is performed.

In addition to its role in regulating on-line motor behavior, the cerebellum also contributes to functions related to motor learning as well as other complex behaviors which are not movement related. The specific role the cerebellum plays in these higher order functions is still a matter of discussion. Similar to its role in regulating movements, its role in higher order functions may also be task- and condition-dependent. Consequently, its specific contribution to storing motor engrams and in regulating the storage-related processes at other sites remains uncertain and may be dependent on the type of behavior being learned and the conditions under which the task is being performed. Its role in other non-motor functions has been inferred largely from testing cerebellar patients and from imaging studies. The current evidence clearly shows that activity in certain cerebellar regions is modulated during the performance of certain higher order tasks, and that some complex higher order functions are impaired in cerebellar patients [6].

Many questions remain regarding the precise mechanisms by which the cerebellar cortex and nuclei contribute to the multiple types of neuronal and system interactions required for the execution of the wide variety of behaviors in which this structure is involved. Attaining the answers to these questions is confounded not only by the complexity of the integration required but also by the fact that the extent of the cerebellum's involvement in both the on-line control of movement and higher functions associated with motor control appear to be task- and/or condition-dependent. Thus, the extent and the nature of the cerebellum's involvement in any given movement is likely dependent on factors such as: the type or class of movement (reflexive, volitional, postural, etc.), the characteristics of the motor sequence, the novelty of the movement, the extent to which learning is required, the association of posture and movement, the occurrence of a perturbation during execution, and the requirement of feedforward and/or feedback control.

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Cerebellar Hemisphere

Synonyms
Hemispherium cerebelli; Hemisphere of cerebellum

Definition
The cerebellum can be divided into three parts:

- Hemispheres (cerebellar hemisphere)
- Vermis cerebelli
- Peduncles (cerebellar peduncles)

The hemispheres have a pronounced cortical structure (cerebellar cortex) rising like a tree from the central matter (medullary body of cerebellum) and is called arbor vitae, the tree of life.

►Cerebellum

Cerebellar Hemisphere, Intermediate Part

Definition
The regions of the cerebellar hemisphere that are close to the vermis are called the cerebellar hemisphere, intermediate part. This runs around 1 cm to the right and left of the vermis, and like the latter it receives its afferents primarily from the spinal cord (spinocerebellum). As opposed to the vermis, the Purkinje cells of the intermediate part project to the interpositus nucleus and not, as in the case of the vermis, to the fastigial nucleus.

►Cerebellum

Cerebellar Hemisphere, Lateral Part

Definition
The cerebellar hemisphere is subdivided into the intermediate part close to the vermis and the remaining lateral part. This has resulted from important functional observation, indicating that the Purkinje cells located in this lateral part have a common projection area, i.e. the dentate nucleus, while conversely the Purkinje fibers of the of the cerebellar hemisphere, intermediate part, project to the interpositus nucleus.

►Cerebellum

Cerebellar Hemorrhage

Definition
Cerebellar hemorrhage often occurs around the ►dentate nucleus and causes ►atasia-abasia and ipsilateral limb ►ataxia. Sometimes there is ipsilateral facial weakness and gaze palsy. With increasing swelling, ►coma, ►miosis, ►ophthalmoplegia and disturbances of respiration may occur and end in demise.

Cerebellar Long-Term Depression

Definition
Long-term depression is a type of synaptic plasticity accompanied with the long-lasting decrease in efficacy of synaptic transmission. In the cerebellar cortex, repetitive coupled activation of parallel fibers and a climbing fiber induces the long-lasting decrease of transmission efficacy at the parallel fibers and Purkinje neuron synapses. This cerebellar long-term depression has been considered as a cellular basis of motor learning.

►Sensory Motor Learning/Memory and Cerebellum

Cerebellar Nuclei

Definition
A set of three discrete nuclei within the cerebellum consisting of medial, intermediate and lateral nuclear groups. These nuclei receive inputs from extrinsic sources and from cerebellar Purkinje cells from different regions of the cerebellum. The axons of cerebellar nuclear neurons project to the brainstem and thalamus.

►Cerebellar Functions
►Purkinje Cell, Neuron

Cerebellar Nuclei

Synonyms
Nuclei cerebelli; Cerebellar nuclei

Definition

Subsumed under this collective term are four central cerebellar nuclei:

- Dentate nucleus
- Fastigial nucleus
- Emboliform nucleus
- Globose nucleus

►Cerebellum

Cerebellar Sagittal Zone

Definition

An anterior-posterior strip of the cerebellar cortex containing Purkinje cells projecting to a specific mediolateral region in the cerebellar nuclei. Each zone also receives projections from a specific region of the inferior olive. There are also chemical markers that demarcate these zones.

►Cerebellar Functions
►Purkinje Cell, Neuron

Cerebellum

Definition

Cerebellum is composed of a centrally situated vermis ("worm") and the two hemispheres. It is responsible above all for planning motor programs and for preserving equilibrium.

Cerebellum – Flocculus Target Neurons

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Synonyms

FTNs

Definition

Neurons in the cerebellar roof nuclei or brainstem that receive the terminals of cerebellar cortical Purkinje cells.

Characteristics

Quantitative Description

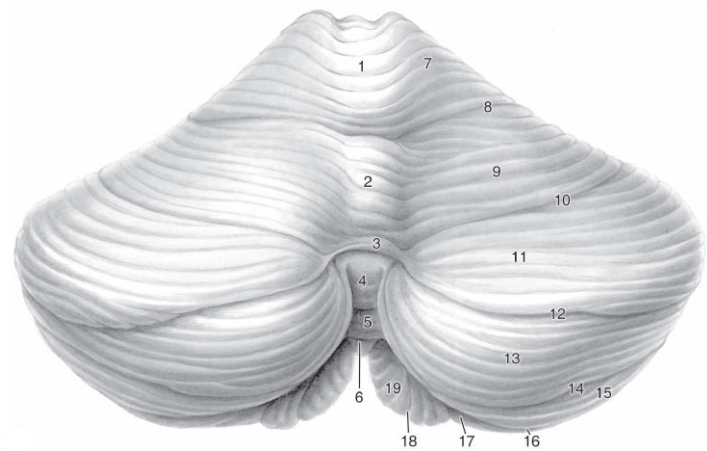
FTNs are usually only one or two synapses distant from the motor output. Thus, while Purkinje cells receive mixed sensory and motor signals, FTNs tend to be more related to the motor system. FTNs receive the terminals of cerebellar cortical Purkinje neurons, usually upon their somata and proximal dendrites. This results in powerful mono-synaptic inhibition that is also tonic, as the average firing rate of a Purkinje cell, at least in the cerebellar ►flocculus, is about 100 impulses/s. FTNs, in turn usually fire at high rates, ca. 120 impulses/s because they are bombarded by excitatory inputs (►Flocculus hypothesis). This balance between FTN afferent excitation and Purkinje cell inhibition determines the moment-to-moment firing rate of FTNs.

Higher Level Structures

The head can be envisioned as a sphere mounted on a ball joint, the neck, and is thus free to rotate in pitch, roll, and yaw. The head and body can also translate linearly. (An example of linear translation is walking.) The brain needs to be kept informed of the linear motion and position of the head and body and of the angular motion of the head. Relevant information is carried by the primary vestibular afferents that originate within the vestibular labyrinth. The labyrinth, located within the inner ear, is composed of linear accelerometers that sense the impulsive and gravitational components of linear acceleration and angular accelerometers that sense angular head motion. The angular sensors, the semicircular canals, are three in number bilaterally, and anatomically situated in the pitch, roll, and yaw axes of head rotation. Primary vestibular afferents terminate within the vestibular nuclei in the brainstem, while a subset projects directly to the cerebellum. Fig. 1 illustrates these neural connections.

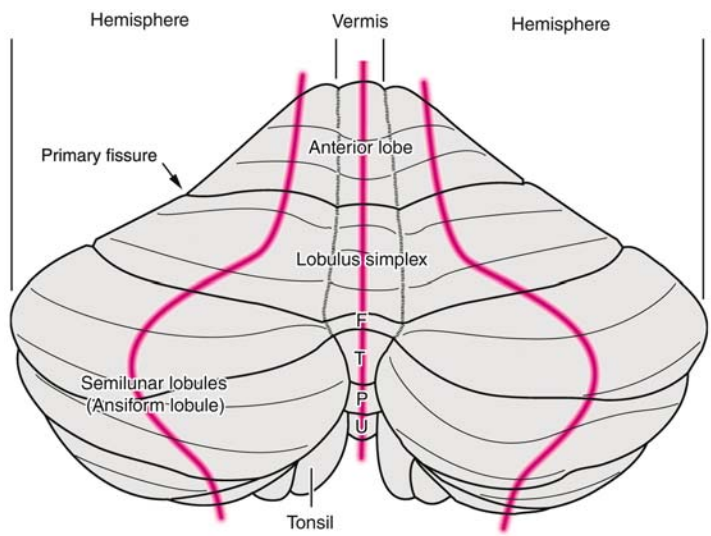
The brainstem terminal sites of primary vestibular afferents define the territory of the vestibular nuclei. Some vestibular nuclear neurons send their (axons) nerve fibers to the cerebellum. These are called flocculus projecting neurons or FPNs (Fig. 1), and relay information about head motion and position that originates within the labyrinth. The vestibular nuclei are often viewed as a subset of the cerebellar roof nuclei (fastigial, interpositus, and dentate nuclei) because of the volume of vestibulo-cerebello-vestibular impulse traffic.

The sole output of the cerebellar cortex is the axons of the Purkinje cell, and while the terminal sites of these axons are localized to certain nuclear sites, they can also be diffuse in other regions. Thus, there is no specific,



1 Culmen
2 Declive
3 Folium vermis
4 Tuber vermis
5 Pyramis
6 Uvula
7 Quadrangular lobule
8 Primary fissure
9 Lobulus simplex
10 Posterior superior fissure
11 Superior semilunar lobule
12 Horizontal fissure
13 Inferior semilunar lobule
14 Pregracile fissure (variable)
15 Gracile lobule
16 Prebiventral fissure
17 Biventral lobule
18 Secondary fissure
19 Tonsil

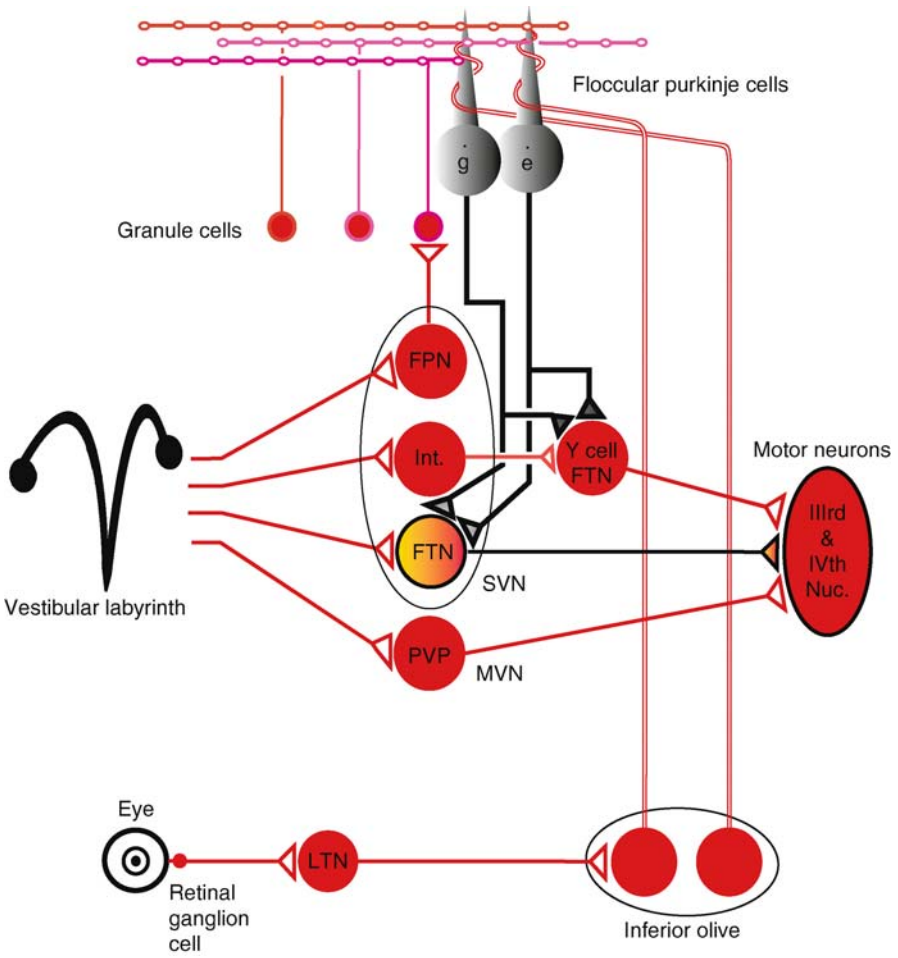
Cerebellum. Figure 1a Dorsal view of the cerebellum (6/5×). Original figure 3.11a and b; taken from Nieuwenhuys, R; Voogd, J; van Huijzen, C. (Eds) 2008 "The Human Central Nervous System". Fourth Edition. Springer, Berlin. page 83 with permission.



Cerebellum. Figure 1b Diagram of a dorsal view of the cerebellum. The direction of the folial chains of vermis and hemispheres is indicated by *red lines*. Note folial loop of the semilunar lobules. (The ansiform lobule of the comparative anatomical nomenclature, see also Fig. 20.2) *F*, folium; *P*, pyramis; *T*, tuber; *U*, uvula; taken from Nieuwenhuys, R; Voogd, J; van Huijzen, C. (Eds) 2008 "The Human Central Nervous System". Fourth Edition. Springer, Berlin. Page 83 with permission.

anatomical vestibulo-cerebellar territory. The vestibulo ocular reflex or VOR can serve as an example system to illustrate some principles of vestibular, cerebellar interactions.

VOR circuitry, although touted as a simple system because of the three-neuron arc, from vestibular nerve input to oculomotor neuron output, is actually decidedly more complex. This arc is imbedded into a structure



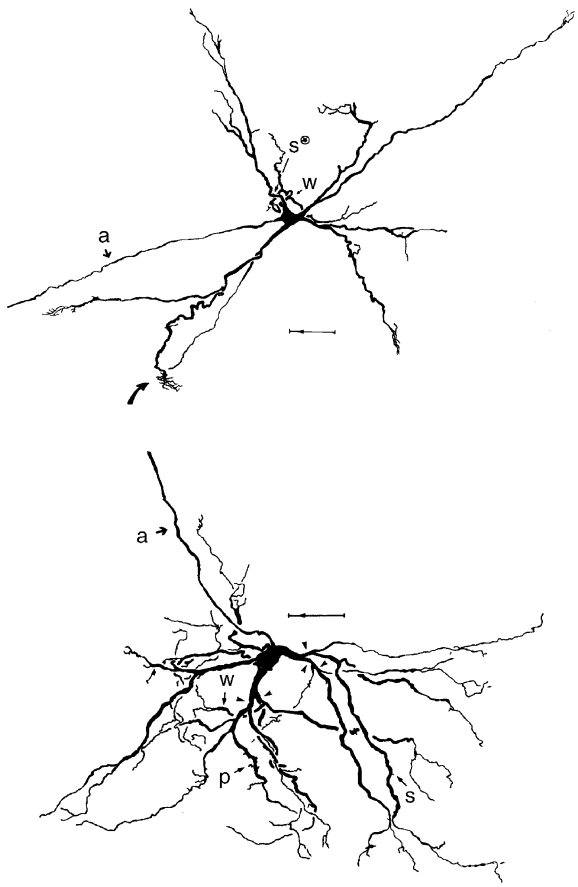
Cerebellum – Flocculus Target Neurons. Figure 1 A schematic of the connections between the flocculus of the cerebellum and brainstem that control the VOR. FTN is a flocculus target neuron, FPN is a flocculus projecting neuron, PVP is a position-vestibular-pause neuron, Y Cell is a cell in the Y group of the vestibular nuclei, Int. is an interneuron, SVN is a superior vestibular nucleus, MVN is a medial vestibular nucleus, IIIrd and IVth nuc. are the oculomotor and trochlear nuclei, respectively.

containing highly recursive and interconnected loops between the brainstem and cerebellum. Inputs to the cerebellum via FPNs of the vestibular nuclei transmit head velocity and eye movement parameters to the cerebellar cortex carried by mossy fibers. This information is processed within the cortical circuitry and the output of the computation is returned to the vestibular nuclei by Purkinje axons that terminate on a subset of nuclear neurons, the FTNs (Fig. 1). VOR-FTNs generally project directly to extraocular motor neurons, the output of the three-neuron arc. Due to this anatomy, Ito, [1] more than 30 years ago, envisioned the flocculus as a side loop of the main VOR circuitry. While VOR-FTNs are the most intensely studied, it should be realized that the cerebellar cortex also projects to many other nuclei such as Deiters' nucleus, the dorsal, and the lateral vestibular nucleus. Giant Deiters' neurons receive some primary afferent vestibular input, are the recipient of anterior lobe Purkinje axons, and give rise to the lateral vestibulo-spinal tract that terminates upon spinal extensor motor neurons. Fastigial nucleus neurons are also the targets of cortical Purkinje cell axons and are involved in the formation of saccadic and smooth pursuit eye movements. There is also major cerebellar projecting and recipient traffic within the descending and medial vestibular nuclei that has not yet been the object of much study, but is likely involved in velocity storage and oculomotor integration.

Lower Level Components

The somadendritic morphology of vestibular neurons is correlated with their axonal projection targets. Vestibular VOR neurons project rostrally to the oculomotor nuclei and to the cerebellum. Many superior vestibular nucleus (SVN)-VOR neurons are FTNs. Mitsacos et al. [2,3] injected SVNs neurons with horseradish peroxidase for

morphological study. Cells were identified as projecting to the oculomotor nuclear complex (VOR-SVN) or to the cerebellum. VOR-SVN neurons vary in shape from pyramidal or multipolar to ovoidal or elongated. Most neurons exhibited their longest dendritic extent along the rostro-caudal axis while their shortest extent was in the coronal plane. Most of the dendrites remained within the cellular boundaries of the nucleus. The branching pattern of VOR neurons is isodendritic [4] i.e. most dendrites follow a straight course and branch in such a manner that the primary dendritic segments are shorter than the secondary ones and these, in turn, are shorter than the tertiary ones. Fig. 2 illustrates examples of FPN and VOR neurons. Note the differences in dendritic trees.



Cerebellum – Flocculus Target Neurons.
Figure 2 Reconstructions of two superior vestibular nucleus neurons. The upper neuron is the soma and dendrites of an SVN-VOR neuron. The curved arrow points to a terminal dendritic formation, s is a dendritic spine, w is a wavy dendrite and a is the axon. The bottom neuron is an SVN-cerebellar projecting neuron. Arrowheads point to dendritic segments displaying an allodendritic branching pattern, p is a dendritic process, and w is a wavy dendrite. Calibration is 100 μm; arrow in the calibration bar points to the midline.

Cerebellar-projecting neurons had dendrites also confined to the SVN cellular boundaries and demonstrated the same rostro-caudal orientation as VOR neurons. While on average only 16% of VOR neuronal dendrites exhibited an allodendritic branching pattern (daughter branches shorter than parents, resulting in a dendritic arborization that is denser towards the periphery of the dendritic tree), neurons projecting to the cerebellum exhibit a particularly high degree of allodendritic branching. In the Squirrel monkey, SVN-VOR and cerebellar projecting neurons are morphologically similar to those described in the cat [5].

The cerebellar-brainstem loop has long been implicated in VOR plasticity, smooth pursuit eye movement generation, and the oculomotor integrator. Removal of the cerebellum completely abolishes the ability to change VOR gain, severely compromises smooth pursuit eye movements and affects the ability to hold gaze at eccentric positions.

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Cerebellum – Oculomotor Vermis

Definition

The circumscribed portion of the cerebellar vermis (lobules VIc and VII) that appears to be integral to the control of saccadic and smooth-pursuit eye movements.

►Cerebellum – Role in Eye Movements
►Oculomotor Vermis
►Saccade, Saccadic Eye Movement
►Smooth Pursuit Eye Movements

Cerebellum – Role in Eye Movements

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Synonyms

Oculomotor cerebellum; Vestibulocerebellum

Definition

As with other motor systems, circumscribed parts of the cerebellar cortex and deep cerebellar nuclei participate in the generation and control of eye movements. These eye movements include ►saccades, smooth pursuit (►smooth pursuit eye movements), the ►vestibulo-ocular reflex (VOR), and ►vergence [1]. Visual and vestibular signals and oculomotor command signals arise from relay nuclei in the brainstem, are processed in the cerebellum, and project back to the brainstem where they are ultimately conveyed to the ocular motor nuclei. Such trans-cerebellar pathways that mediate the generation of saccades and the VOR each parallel a more direct pathway confined to the brainstem, as is typical of other motor systems. However, trans-cerebellar pathways that mediate the generation of smooth pursuit do not appear to have a direct counterpart in the brainstem.

Characteristics

Parts of the Cerebellum

The ►oculomotor vermis (►cerebellum – oculomotor vermis) consists of lobules VIc and VII of the midline cerebellar cortex. It was first defined in the monkey as the region where low amplitude (<10 μA) electrical microstimulation elicits saccadic eye movements, but slower, smooth-pursuit like eye movements are also elicited. Prominent saccade, smooth-pursuit, and head-movement related signals are present in the discharges of neurons in this region [2]. Nearby regions that are not in the circumscribed oculomotor vermis (e.g. vermal lobules VIa,b and VIII) may nonetheless participate somewhat in the control of eye movements, since eye movements can be elicited in this area by microstimulation at moderate current strengths, and eye- and head-movement neuronal discharges can also been recorded.

The ►fastigial oculomotor region (FOR) (►cerebellum – fastigial oculomotor region (FOR)) is a circumscribed region in the caudal fastigial nucleus, the most medial of the deep cerebellar nuclei, where saccades are elicited by microstimulation and where neurons exhibiting saccade-related and smooth-pursuit related discharges are found. This region corresponds closely with the part of the fastigial nucleus that receives Purkinje-cell input from the oculomotor vermis.

The ►flocculus and ventral paraflocculus are contiguous structures adjacent to the cerebellar hemispheres and overlying the eighth cranial nerve. Due to past inconsistencies in the naming of the ventral paraflocculus and to similarities of its connections and neuronal discharges with those of the flocculus (see below), the two areas are sometimes lumped together as the ►floccular lobe. Collectively, they participate in the generation of smooth pursuit and the regulation of the VOR. The flocculus receives direct input from the vestibular portion of the eighth nerve, and so is one part of the vestibulocerebellum.

The nodulus and uvula are vermal regions on the underside of the cerebellum that corresponds to midline lobules X and IX, respectively. The nodulus and rostral uvula also receive direct input from the vestibular nerve and have heavy reciprocal connections with the vestibular nuclei. It is the second component of the vestibulocerebellum. The nodulus/uvula is integral to the velocity storage mechanism, and so, participates in controlling the time course and direction of prolonged vestibularly and optokinetically induced eye movements (see ►velocity storage).

The ventral portion of the monkey posterior interpositus nucleus and adjacent portions of the caudal dentate nucleus have been implicated in the control of saccades. Inputs to this area derive from saccadic and/or smooth-pursuit regions of parietal cortex by way of the dorsal and dorsolateral pontine nuclei. The same inputs innervate the dorsal and ventral paraflocculus, which project back to the interpositus/dentate. This region also projects directly to the superior colliculus and interstitial nucleus of Cajal, and indirectly to the frontal eye fields; all structures known to participate in the generation of saccades. In addition, the interpositus contains neurons that exhibit saccade-related discharges, and its transient inactivation using the GABA agonist, muscimol, results in an upward bias in the endpoints of saccades (dysmetria). This data is suggestive but preliminary, and a better understanding of the role of the ventral posterior interpositus and dentate area will require additional data.

A second more rostral oculomotor part of the dentate nucleus, which may overlap the part of the first area, is an extension of the y-group of the vestibular complex. This region contains neurons that are excited during upward eye velocity during smooth pursuit and during upward head rotation with the VOR suppressed. In macaques, these eye and head signals are roughly equal, and approximately cancel during VOR in the dark (i.e. they encode ►gaze velocity). Some neurons have eye position sensitivity and most have saccadic eye-movement sensitivity. As the dentate/y-group area receives inputs from the paraflocculus and projects to the oculomotor nucleus, this region is thought to participate in generating vertical smooth pursuit.

Finally, evolution in humans produced a huge expansion of the lateral cerebellum along with its target

nucleus, the dentate. There are strong indications that this expanded region participates in human cognitive functions. Accordingly, a portion of the lateral cerebellum has increased activity in functional-MRI studies of humans generating memory-guided saccades (►memory-guided saccade task) and ►antisaccades.

Higher Level Structures

Oculomotor portions of the cerebellum receive direct input from the eighth nerve, the vestibular nuclei, the pontine reticular formation (paramedian pontine reticular formation (PPRF)), raphe nuclei in the pons and medulla, and indirectly from the superior colliculus and specific regions of the cerebral cortex. The latter are relayed through the ►nucleus reticularis tegmenti pontis (NRTP) and the pontine nuclei (see below). The cortical inputs to these relay nuclei include the ►frontal eye fields (FEF), the ►supplementary eye fields (SEF), parietal areas middle temporal (MT), medial superior temporal (MST), and ►lateral intraparietal area (LIP). (Each of these areas is discussed more fully elsewhere in this Encyclopedia). A previous concept that each cortical region served one particular type of eye movement, (e.g. the FEF subserved saccades and area MST subserved smooth pursuit) has been replaced after the demonstration that the FEF, SEF, and LIP each have adjoining or partially overlapping saccade-related, smooth-pursuit related, and sometimes vergence-related areas, and that visual motion processing areas MT and MST have connections with the saccade-related as well as pursuit-related cortical and subcortical structures. Accordingly, both saccade-related, smooth-pursuit related and vergence-related signals have been recorded from neurons in NRTP and the dorsolateral pontine nuclei.

The inferior olive provides climbing fiber inputs to all portions of the contralateral cerebellum, but these inputs are not thought to be important in short-term signal processing and will not be considered further.

Lower Level Processes

There are several targets of the cerebellar output that are best examined in the context of the pathways mediating each type of eye-movement. For the saccadic system, cerebellar efferents arise from the FOR and project to the saccadic burst generators in the contralateral pontine and midbrain reticular formations, the contralateral superior colliculus, and thalamus. The burst generators excite agonist and inhibit antagonist motoneurons to generate the saccade (see ►brainstem burst generator). For the smooth-pursuit system, different fastigial-nucleus efferents project to the vestibular nuclei and the pontine and midbrain reticular formations near the burst generators. An additional smooth pursuit pathway traverses the floccular lobe, which in turn, also projects to the vestibular nuclear complex. Specific output targets, which are better known for the floccular pathway, include the superior vestibular nucleus, the medial vestibular nucleus, the ventrolateral vestibular nucleus, and the y group. Signals are then conveyed to the ocular motoneurons to produce smooth-pursuit eye movements. There is also a projection of the floccular lobe to the basal interstitial nucleus of the cerebellum, whose function is not known. Details regarding these pathways are elaborated for each eye-movement system below.

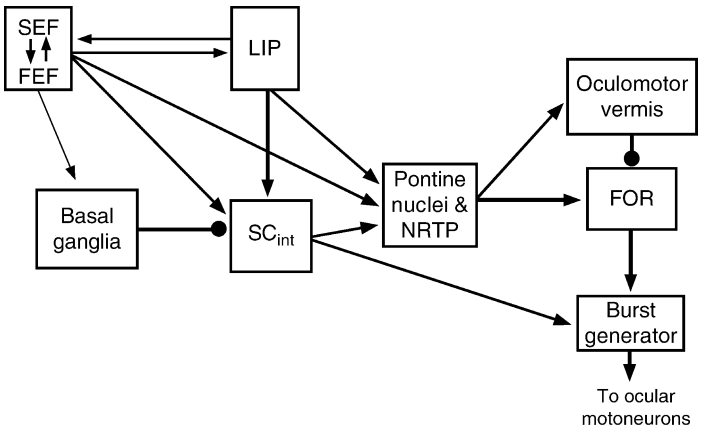
Functions of the Cerebellum

Generation and Control of Saccades

Preliminary commands for the generation of saccades originate in cortical areas that include the FEF, SEF, LIP, and the ►substantia nigra. These signals converge on the deep and intermediate layers of the ►superior colliculus, which issues the final command to generate a saccade (Fig. 1). Crossed collicular efferents convey this command directly to the ►brainstem burst generator and indirectly to the cerebellum via medial parts of NRTP. In addition, the FEF and SEF have direct ipsilateral projections to medial and dorsal NRTP and to the medial and dorsolateral pontine nuclei, while LIP has direct projections to the dorsolateral pontine nuclei. These areas of NRTP and the pontine nuclei in turn send projections to the fastigial oculomotor region (FOR) and to the oculomotor vermis bilaterally. Purkinje cells in the oculomotor vermis project to the FOR, which in turn projects to the saccadic burst generator. Thus, the burst generator receives a direct saccadic command from the superior colliculus and an indirect one via the cerebellar loop. Present thinking is that the former is a course command that is refined by the output of the cerebellum to achieve more precise control of saccade size and direction. Moreover, it is thought that this refined signal is the product of adaptive motor learning regulated by the cerebellum (see ►saccadic adaptation).

Purkinje cells in the oculomotor vermis have a spontaneous discharge, and the majority exhibit saccade-related responses [3]. Of these, the great majority (71–97%, depending on the study) exhibit a burst of spikes during or preceding saccades in at least one direction, while the remainder cease or reduce their firing during or preceding the saccade. Of the neurons that burst, most have a burst that precede saccades in one direction and have a later burst in the opposite direction. Others have no directional preference, while others burst in one direction and pause in the opposite direction. Directional preferences can be either ►ipsiversive or ►contraversive, with a slight contraversive preference. The duration of the Purkinje cell burst is, on average, correlated with the duration of the saccade, and may serve to control saccade duration [4].

Purkinje cells in the oculomotor vermis make inhibitory connections with neurons in the ipsilateral FOR. However, the saccade-related discharges of FOR



Cerebellum – Role in Eye Movements. Figure 1 Block diagram of the saccadic system showing cortical input converging on the intermediate and deep layers of the superior colliculus (SC_{int}) and on to precerebellar relay nuclei in the ventral pons (NRTP and Pontine Nuclei). These relay nuclei also receive a copy of the saccadic command from the SC_{int}, and all signals are sent to the oculomotor vermis and the fastigial oculomotor region (FOR). The major fed-forward pathways are shown; feedback pathways from the cerebellum to NRTP, from cerebellum to the thalamus, and from thalamus to cortex, have been omitted. Thinner lines represent pathways not discussed in the text. Lines ending in arrow-heads represent excitatory connections; lines ending in circular bulbs represent inhibitory connections. *FEF*, frontal eye fields; *SEF*, supplementary eye fields; *LIP*, lateral intraparietal area; *NRTP*, nucleus reticularis tegmenti pontis.

neurons resemble those of the vermis more than their inverse (see below). Evidently, FOR neurons are strongly influenced by the collaterals of the same ►mossy-fiber afferents that provide input to the vermis. FOR neurons typically have a spontaneous firing rate and a burst of spikes for all saccades, but the timing is characteristically dependent on saccade direction. Bursts for contraversive saccades typically lead saccade onset by an average 4–19 ms [5], and end about the same time as the saccade. The burst onset for ipsiversive saccades typically lag saccade onset but lead saccade termination, and the burst typically outlasts the saccade. The loose correlation between ipsiversive burst onset and saccade termination has led to the idea that this burst may bring about saccade end. The bursts are frequently preceded by decreases in firing or frank pauses, especially for ipsiversive saccades, and sometimes are followed by pauses. These pauses are possibly the work of inhibition from the vermis, and may reflect a process of sculpting the leading and trailing edges of the FOR bursts. Presumably, the vermis also affects the peak burst frequency of FOR neurons.

A minority of FOR-neurons have a qualitatively similar discharge pattern that is rotated into a predominantly vertical direction.

Efferents of the FOR target the horizontal and vertical burst generators, and physiological data show that efferents make excitatory connections with horizontal burst neurons (see ►brainstem burst generator). Based on these connections, the discharges of FOR neurons, and the effect of unilateral lesions (see below), the FOR appears to augment the discharge frequency of the premotor ►excitatory burst neurons (EBNs) during contraversive saccades, and may assist in terminating the discharge of excitatory burst neurons during ipsiversive saccades. By having such control of the burst duration and amplitude of the agonist and antagonist premotor neurons, the FOR is well suited to exert powerful control over saccade size and direction.

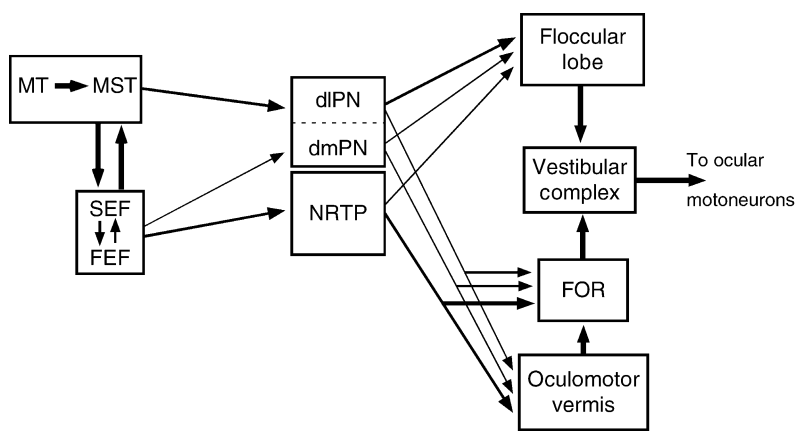
Generation of Smooth Pursuit

Smooth pursuit is initiated by the decision to track a moving target or the perception of motion without frank motion. Little is known about the neural substrate of the decision or the perception, but the encoding of target motion by striate and extrastriate visual cortex is well understood. In particular, cortical areas MT and MST are thought to be the source of the target motion signal used by the smooth-pursuit system. Medial parietal area 7m may also participate, but there is currently insufficient data to be positive. These regions project to the dorsolateral pontine nuclei, the frontal eye fields, and the supplementary eye fields, which each contain regions dedicated to smooth pursuit (see ►frontal pursuit area). The FEF and SEF, in turn, project principally to the medial, dorsal, and dorsolateral pontine nuclei and to medial and dorsal NRTP. These pontine precerebellar nuclei convey the highly processed visual information to two different cerebellar circuits which are both important for the generation of smooth pursuit [6].

Medial Cerebellar Circuit

The first circuit includes the oculomotor vermis and caudal fastigial nucleus in a pathway very reminiscent of the saccade-related circuit above (Fig. 2). FEF- and SEF-recipient regions of medial and dorsal NRTP and dorso-medial pontine nuclei, and parietal-recipient regions of the dorsolateral pontine nuclei project to the oculomotor vermis and to the caudal fastigial nucleus via collaterals. Electrophysiological studies of Purkinje cells in the oculomotor vermis have yielded highly variable results, so the following description will not be quantitative. The majority of cells are excited during movement of the eye in a characteristic preferred direction that varies from cell to cell. Substantial numbers of these Purkinje cells also respond to image motion across the stationary retina and/or to vestibular stimulation in the absence of eye movements (subjects suppress their VOR during whole-body oscillation by fixating a target that moves in conjunction with their head). Eye-movement and vestibular responses are in phase with eye and head velocity, respectively. Many Purkinje cells have eye- and head-velocity sensitivities that are quantitatively similar and are in the same direction ("►gaze-velocity neurons"). These gaze-velocity signals are likely a combination of processed visual signals being shaped into a smooth-pursuit command, eye-velocity signals, and head velocity signals that are input by way of projections from the brainstem. A smaller number of Purkinje cells have eye- and head-velocity sensitivities that are substantially unequal or in different directions. According to some studies, many eye- and head-velocity signals can also be recorded from vermal areas of lobules VIa,b and VIII, which are immediately adjacent to the oculomotor vermis.

Purkinje cells in the oculomotor and surrounding vermis project to the caudal fastigial nucleus. Additionally, the fastigial nucleus receives input from NRTP, the dorsolateral and dorsomedial pontine nuclei, as noted above. Smooth-pursuit neurons in the fastigial nucleus exhibit discharges reminiscent of those in the vermis, with almost all exhibiting head-velocity and eye-velocity sensitivity [7]. However, the head-velocity and eye-velocity sensitivities were usually different in phase and magnitude, so that the neurons did not exhibit gaze-velocity discharges. There was also a large preponderance of neurons preferring contraversive and downward eye movement. During sudden-onset smooth pursuit, the latency of the response sufficiently preceded eye acceleration to support the hypothesis that the caudal fastigial participates in the initiation of smooth pursuit. The bias in preferred directions together with the effect of transient inhibition of caudal fastigial neurons by injection of muscimol has led to the idea that caudal fastigial neurons appear to assist in promoting contraversive eye acceleration and ipsiversive eye deceleration [1]. The smooth-pursuit related neurons in the caudal fastigial constitute a substantially separate population from the saccade-related neurons, since only 29% of the neurons discharged during saccades.



Cerebellum – Role in Eye Movements. Figure 2 Block diagram of the smooth pursuit system showing the flow of target-motion information from cortical areas MT and MST to cortical areas FEF and SEF, from the cortex to relays in the ventral pons (dlPN, dmPN, NRTP), and then to the cerebellum via two routes (Floccular lobe and Oculomotor vermis). Signals converge on the vestibular nuclei, which drive the ocular motoneurons. Thinner lines represent weaker pathways. *MT*, middle temporal; *MST*, medial superior temporal; *FEF*, frontal eye fields; *SEF*, supplementary eye fields; *dlPN*, dorsolateral pontine nuclei; *dmPN*, dorsomedial pontine nuclei; *NRTP*, nucleus reticularis tegmenti pontis; *FOR*, fastigial oculomotor region. The vestibular complex includes the medial, superior, and ventrolateral vestibular nuclei and the y group. Only major fed-forward pathways are shown; feedback pathways from the cerebellum to NRTP and the thalamus have been omitted.

The exact pathway by which fastigial smooth-pursuit signals reach ocular motoneurons has not been adequately explored. Efferents of the caudal fastigial nucleus target the vestibular nuclei in addition to the ►paramedian pontine reticular formation. Parts of the vestibular nuclei contain neurons that encode eye position and/or velocity during smooth pursuit and that project to the abducens nucleus. There are also neurons in the reticular formation that encode eye position and/or velocity, but their projections are unknown.

Floccular Smooth-Pursuit Pathway

The floccular lobe receives information from some of the same areas as does the oculomotor vermis. Processed visual information originating in parietal cortex is conveyed to the floccular lobe via the dorsolateral and dorsal pontine nuclei. Smooth-pursuit signals originating in the FEF and SEF are conveyed via medial NRTP and medial pontine nuclei (Fig. 2). In addition, the floccular lobe receives eye- and head-movement signals from the vestibular nuclei, and eye-movement signals from raphe and paramedian structures in the pontine reticular formation.

The ventral paraflocculus receives the bulk of the projections from the pontine nuclei, while the flocculus *per se* receives a heavier projection from the vestibular nuclei. This has lead to the hypothesis that the ventral paraflocculus is more specialized for generating smooth-pursuit commands, while the flocculus is more specialized for controlling the VOR [8]. Nonetheless, the signals recorded from neurons in both regions differ only in minor ways. The flocculus is further subdivided into three parasagittal "zones". A middle zone exhibits neural signals related to horizontal eye- and head-movements and is most strongly connected to the medial vestibular nucleus, which preferentially mediates horizontal eye movements. Two surrounding zones exhibit signals related to vertical eye- and head-movements and are most strongly connected to the superior vestibular nucleus and y group, which preferentially mediate vertical eye movements.

Eye- and head-movement signals recorded from Purkinje cells in the floccular lobe resemble those recorded from the oculomotor vermis. The predominant group of neurons exhibit horizontal or vertical gaze-velocity discharges [9]. As described earlier, the gaze-velocity discharge could be a smooth-pursuit command first constructed in higher centers, but the prevalence of eye-position, eye-velocity, and head-velocity input signals conveyed on ►mossy fibers [9] from the pontine reticular formation and the vestibular nuclei makes it likely that these latter signals also contribute to the firing of gaze-velocity neurons. In fact, an eye-movement corollary discharge fed back to the flocculus forms the basis of one hypothesis about the generation of predictive smooth-pursuit. In squirrel monkeys, the "gaze-velocity" neurons have a sensitivity to eye velocity that is twice the sensitivity to head velocity. Moreover, all monkey species have another large group of Purkinje cells encode eye position and eye velocity. Altogether, there is a surfeit of eye-velocity information that makes it difficult to explain how the floccular lobe both produces smooth pursuit and suppresses the VOR.

The floccular lobe conveys the smooth pursuit command to the motoneurons via the vestibular nuclei. Horizontal Purkinje-cell (►Horizontal-gaze-velocity purkinje cells) efferents impinge upon known "flocculus target neurons" in the medial vestibular nucleus and more weakly upon secondary vestibular neurons in the ventrolateral vestibular nucleus. Some flocculus target neurons make direct connections with abducens motoneurons while others make indirect connections. Vertical Purkinje-cell efferents synapse in the superior vestibular nucleus and in the y group, both of which project to motoneuron pools in the oculomotor nucleus that subserve vertical eye movements.

VOR

As stated earlier, the floccular lobe receives a major input from the vestibular nuclei and the flocculus *per se* receives direct input from the vestibular nerve. This vestibular information presumably contributes to the construction of gaze-velocity signals on floccular Purkinje cells. This heavy input, together with the projections back to portions of the vestibular complex that influence ocular motoneurons, puts the floccular lobe in a good position to affect the ►gain of the VOR. Probable uses of this capability include increasing VOR gain with increasing convergence of the eye (see ►VOR), and adaptive long-term modulation of VOR gain by plastic mechanisms (see ►VOR adaptation).

Vergence

Neurons responding to pure vergence and/or combinations of version and conjugate eye movements have been found in the oculomotor vermis, the fastigial nucleus, the interpositus nucleus, and in the floccular lobe. The origin of these signals is likely from vergence areas in the superior colliculus and near the frontal eye fields, conveyed by way of NRTP. Thus, it is likely that these structures play a role in producing vergence eye movements, but much research is needed to be more precise.

Pathology

Experimental lesions of the midline cerebellum (oculomotor vermis and caudal fastigial nucleus) produce substantial deficits in saccade generation and in smooth pursuit. Saccade deficits are more pronounced with lesions or chemical inactivation of one side. Inactivation of the caudal fastigial nucleus causes

ipsiversive saccades to overshoot the target by up to a factor of two, and contraversive saccades to undershoot the target by as much as half. Unilateral lesions or inactivation of the oculomotor vermis cause reversed effects. Vertical saccades are misdirected for both types of lesions. Bilateral lesions cause smaller and more balanced ►saccadic dysmetria [1]. Smooth pursuit is similarly affected. Unilateral fastigial inactivation increases ipsiversive eye acceleration for ramp targets up to two times normal, and decreases contraversive acceleration as much as 30%. Bilateral inactivation of the FOR or lesions of the vermis decreased smooth-pursuit gains by 30–50% when subjects track periodic stimuli [1]. The residual smooth pursuit reflects the fact that the FOR/oculomotor vermis is only one of at least two smooth-pursuit pathways, and that pursuit is a closed-loop system.

Experimental lesions of the flocculus and ventral paraflocculus together produce a 50–60% deficit in smooth pursuit and in suppression of the VOR. The gain of the VOR in the dark is affected very little. The ability to hold eccentric gaze is severely affected, as the eye returns towards a neutral point with a ►time constant around 2 s. This has been interpreted as disruption of the velocity-to-position integrator (see ►Neural Integrator) by loss of a high-gain feedback loop through the flocculus.

Localized cerebellar lesions in humans caused by infarcts, tumors, surgery, head trauma, or degenerative disease produce the same symptoms. However, such lesions are rarely as well confined as experimental lesions, so humans exhibit additional eye-movement disorders. These include several different forms of gaze deviations or inability to hold eccentric gaze and nystagmus [10].

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Cerebellum, Zonal Arrangement

Definition

Although the cerebellum features horizontal organization by virtue of its fissures, it is divided functionally into three vertical zones: the central part corresponds to the vermis cerebelli and projects to the fastigial nucleus. The intermediate part is a stip of hemisphere that is less than 1 cm wide to the left and right of the vermis. It projects to the interpositus nucleus. The lateral part, the remaining hemisphere region, projects to the dentate nucleus.

►Cerebellum

Cerebral Cortex

Synonyms

Cortex cerebri

Definition

The cerebral cortex is often referred to simply as cortex. Strictly speaking, this is not correct since the cerebellum also has a cortex.

The cerebral cortex is the thin outer sheet of the forebrain, and contains several layers of nerve cells. Because of its gray color, it is termed “gray matter” as opposed to the “white matter” beneath it, which is made up of fibers (axons) connecting nerve cells in different areas of the brain. The human cortex is 3 mm (0.1 in) thick. According to cytoarchitecture you differentiate Isocortex and allocortex. A more detailed analysis

reveals nearly 50 different cortical areas, the so called Brodmann Areas. The cerebral cortex is divided into five lobes: frontal, parietal, temporal, occipital and limbic lobe. The cerebral cortex is essential for cognition, memory, consciousness, speech and voluntary movement.

►Telencephalon

Cerebral Cortex Development

►Cortical Development

Cerebral Hypoxia

Definition

Transient exposure of brain cells to hypoxia (low oxygen levels), resulting in severe damage, inflammation and degeneration.

Cerebral Meningitis

Definition

Inflammation of the meninges of the brain.

Cerebral Pachymeningitis

Definition

Inflammation of the dura mater of the brain.

Cerebral Palsy

Definition

Cerebral palsy comprises several motor dysfunctions usually resulting from ischemic and/or hypoxic brain injury in the perinatal period. Disorders vary widely depending on the severity of lesions. Mild forms may show ►hyperreflexia and ►Babinski sign, severe forms bilateral ►hemiparesis with spastic posture and gait. An accompanying ►athetosis is frequent.

►Babinski Reflex
►Spasticity

Cerebral Peduncle

Synonyms

Pedunculus cerebri; Cerebral peduncle

Definition

Above the pons are two large, v-shaped parallel fiber bundles, containing efferents descending from the cerebral cortex in the direction of the brainstem and spinal cord. These two strands are called cerebral peduncles.

►Mesencephalon

Cerebral Trunk

Definition

Brainstem. Is composed of the three segments myelencephalon, metencephalon (cerebellum + pons) and Mesencephalon.

►General CNS

Cerebro-cortical Area V1

Definition

The primary visual cortex (also called Brodmann's area 17 and striate cortex), which receives the predominant (but not only) input from the retinas. It was long thought to be the only part of the cortex devoted to vision.

►Striate Cortex Functions
►Geniculo-striate Pathway
►Visual Perception

Cerebro-cortical Area V4

Definition

One of the many cortical visual areas lying outside area V1, and with which it is reciprocally connected, both directly and indirectly. It is specialized for generating color and damage to it leads to the syndrome of cerebral achromatopsia. Together with area V5, it has provided some of the most robust evidence in favor of functional specialization in the visual brain.

►Color Processing
►Extrastriate Visual Cortex
►Visual Neuropsychology
►Visual Perception

Cerebro-cortical Area V5

Definition

One of the many cortical visual areas lying outside area V1, with which it is reciprocally connected. A majority of its cells are responsive to motion and usually in a given direction only. It is thus specialized for visual motion and damage to it leads to the syndrome of cerebral akinetopsia.

►Extrastriate Visual Cortex
►Visual Motion Processing
►Visual Neuropsychology
►Visual Perception

Cerebrospinal Fluid (CSF)

Definition

The fluid surrounding the brain and spinal cord. The CSF is mainly secreted from the epithelial (ependymal) cells of the choroid plexuses in the ventricle, and moves into the subarachnodal spaces through the medial and lateral apertures of the fourth ventricle. The rate of human CSF formation is estimated to be 600–700 ml per day. The total volume of CSF in the subarachnoid spaces and ventricles is about 1,400 ml. Ventricular volume is only about 25 ml. The arachnoid villi are the site through which the CSF is passively transported into the venous flow of dural sinuses. The CSF consists to 99% of water and has a much lower protein concentration (approximately 350 mg L^{-1}) than the serum (70,000 g L^{-1}). Of these proteins only about 10% originate from the extracellular fluid (ECF) drained form the central nervous system (CNS) parenchyma. These may be called "brain specific proteins" and are of particular interest for biomarker research.

Cerebrovascular Accident (CVA)

►Ischemic Stroke

Cerebrovascular Disease

►Ischemic Stroke
►Stroke

Cerebrum (Outer Surface)

Synonyms

Cerebrum (external features)

Definition

At a deep level, is composed of the basal ganglia and peripherally of the greatly folded cerebral cortex, which is subdivided into two hemispheres.

Here all "higher" brain functions such as voluntary motor control, motor and sensory speech, cognition, visual and auditory system, superficial and deep sensibility are processed.

►Telencephalon

Certainty Equivalence

Definition

Certainty Equivalence is a term used in the adaptive control area to indicate that a controller is designed

using current estimated system parameters, as if they were the "true" system parameters.

►Adaptive Control

Cervical Enlargement

Synonyms
Intumescentia cervicalis; Cervical enlargement

Definition
The spinal cord evidences two enlargements: the cervical enlargement in the cervical region and the lumbosacral enlargement in the lumbar region. The fibers of the upper and lower extremities synapse in the enlargements.

Cervico-collic Reflex

Definition
Activation of neck muscles induced by stimulation of neck (cervical) sensory receptors. They induce the contraction of the muscles stretched by a rotation of the head with respect to the body and are aimed at stabilizing the position of the head with respect to the body.

►Vestibulo-spinal Reflexes

Cervico-spinal Reflexes

Definition
Activation of body muscles induced by stimulation of neck sensory receptors, that are particularly represented by muscle spindle afferents in deep, intervertebral muscles. Cervicospinal reflexes acting on the limbs muscles modify the position of the trunk according to the relative position of the head with respect to the body.

They stabilize the position of trunk in space, working together with VS reflexes. Cervicospinal reflexes acting on the neck (cervicocollic) reflexes stabilize the position of the head with respect to the trunk.

►Muscle Spindles
►Proprioception: Role of Muscle Receptors
►Vestibulo-spinal Reflexes

C-fiber Afferent Nerve Fibers

Definition
C-fiber afferent nerve fibers are unmyelinated afferent nerves that conduct action potentials at low velocities (less than 2.5 m/s) and that are often involved in detecting tissue injury or nociceptive stimuli. Activation of these afferents usually triggers painful sensations, neurogenic inflammation and hyperactivity of visceral organs.

►Nociceptors and Characteristics

c-Fos

Definition
c-Fos is a proto-oncogene that belongs to the immediate early gene family of transcription factors. c-Fos is often used as a marker of neural activity.

CFUs-8

Definition
The number of 8-day colony-forming units in spleen of mice, i.e. the parameters of the hemopoiesis.

►Nervous Immune and Hemopoietic Systems: Functional Asymmetry

cGMP

Definition
►Cyclic GMP

cGMP-dependent Protein Kinase (Protein Kinase G)

Definition
A family of serine/threonine protein kinases whose activity are dependent on the level of cGMP in the cell.

Ch1

►Evolution of Subpallial Cholinergic Cell Groups

Ch2

►Evolution of Subpallial Cholinergic Cell Groups

Ch3

►Evolution of Subpallial Cholinergic Cell Groups

Ch4

►Evolution of Subpallial Cholinergic Cell Groups

Chandelier Cell

Definition
The chandelier cell is a distinct morphological type of cerebral cortical interneuron that uses GABA as an inhibitory transmitter. Its axon terminals form a series of boutons linked together by thin connecting pieces, giving the cell a chandelier-like appearance. These terminals end on the initial segments of pyramidal cell axons. The chandelier neuron is also called an axo-axonic cell.

Change in Support Strategy

Definition
A reaction to postural perturbation in which the limbs are moved so as to alter the base of support, i.e. stepping or reaching to grasp or touch an object for support.

►Postural Strategies

Channel Expression

►Intrinsic Properties of Auditory Neurons

Channel Myotonia

Definition
►Myotonia

Channels of Smell

Definition
In the frame of information (or communication) theory, "channel" refers to a link between a source and a receptor allowing data transmission. In olfaction, two channels or sets of channels can be distinguished: the main olfactory system and the accessory olfactory system.

►Chemical Senses

Chaos

Definition
In the field of science and technology, the word chaos usually means deterministic chaos. Nonlinear dynamics

with non-periodicity and sensitive dependence on initial conditions generated not by stochastic process but by deterministic process is called deterministic chaos or simply chaos.

►Neural Networks

Chaotic Neural Networks

Definition

Neuron models with chaotic dynamics are called chaotic neurons. A discrete time chaotic neuron model consists of the terms of the internal states of the external inputs, the feedback inputs, and the relative refractoriness.

Neural network models that are composed of chaotic neurons are called chaotic neural networks. The model of the chaotic neural networks is applied to associative memory networks and combinatorial optimization networks with chaotic dynamics beyond convergent dynamics.

►Neural Networks

Chaperone

Definition

Chaperones are proteins that assist the non-covalent folding/unfolding and the assembly/disassembly of other macromolecular structures, but do not occur in these structures when the latter are performing their normal biological functions.

Chaperones: Protein Trafficking

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Definition

►Chaperones are proteins or protein complexes throughout the cell that aid in the proper folding of nascent polypeptides, promote correct folding of misfolded proteins and target terminally misfolded proteins for degradation. Chaperones are ubiquitous in all tissues and are of specific interest in the nervous system for their role in preventing diseases of neural protein aggregation in conditions such as ►Alzheimer's disease and ►Parkinson's disease.

Characteristics

Chaperones in the Nervous System

The folding of nascent peptides into a specific three-dimensional mature conformation is essential to allow proper function of all proteins. Chaperones are a large family of factors that promote this process, preventing aggregation of misfolded intermediates and by targeting terminally misfolded proteins for degradation. Chaperone mediated ►protein folding is required in all cells and is particularly important in the nervous system, as aberrant protein aggregation of misfolded proteins is a hallmark of many of the major neurodegenerative diseases. Although the majority of proteins fold properly and are quite stable in their functional conformation, different environmental stresses that are placed on the cell can result in unfolding or misfolding of proteins. The neuronal synapse is a particularly challenging area in maintaining proper protein folding conformations due to a dense protein filled cytosol and rapidly changing ion and pH levels. Proteins with abnormal conformations can accumulate over time due to exposure to extrinsic or naturally produced oxidizing agents or environmental stresses and this can result in the protein quality control system being taxed beyond its ability to deal with these misfolded proteins. Therefore, chaperones are thought to play an integral role in the manifestation of neurodegenerative diseases whose common pathological feature is protein aggregates and neuronal cell death.

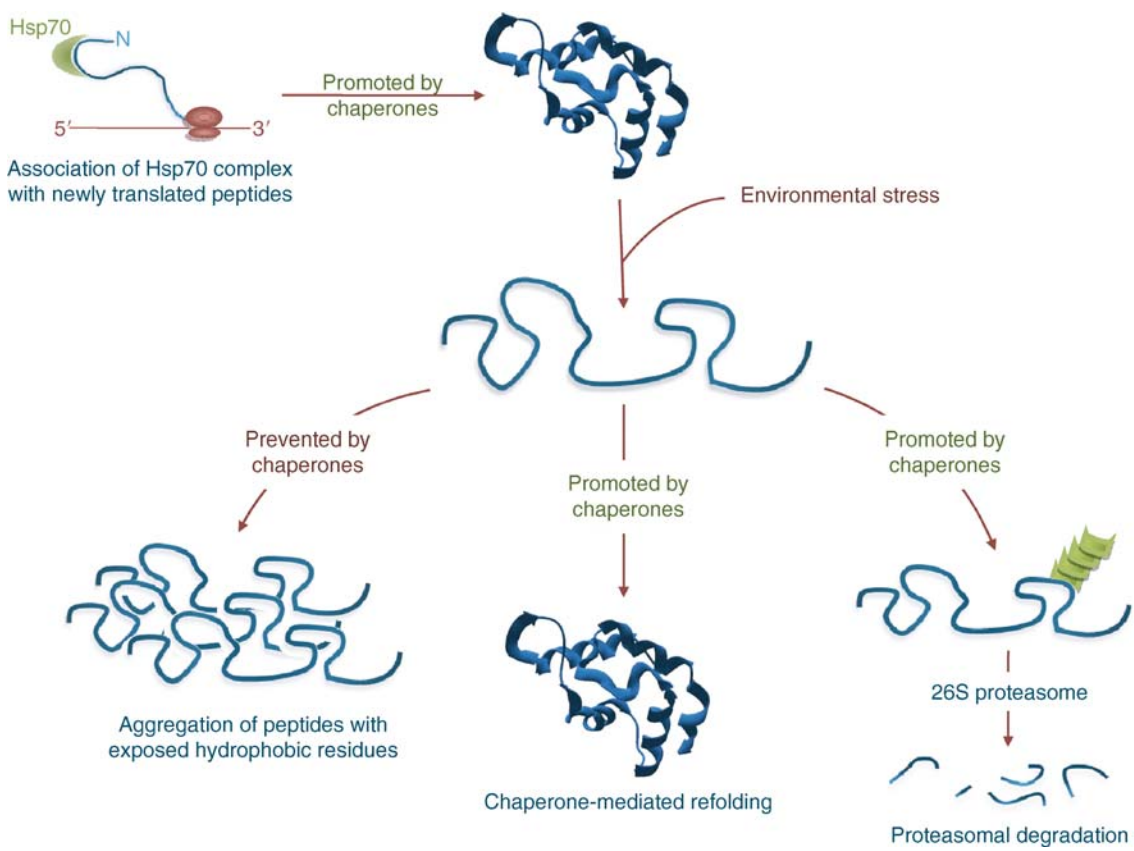
The neuron has long cellular extensions that require transport from the cell body where proteins are made to the dendritic and axonal termini. Synaptic proteins are translated at the cell body and must be transported to the site of action via vesicles that move along the cytoskeleton. A loss in efficiency of vesicle and cellular traffic increases the stress on the protein quality control network at synapses, thus increasing the chance that a toxic aggregation is undetected by the chaperone system. Components of the protein degradation pathway are common at the synapse and associate with endocytic vesicles, suggesting a link between cellular traffic and cytosolic chaperones. Although aggregates are the universal indicator of many neurodegenerative diseases the underlying cellular cause of neuronal loss has many different effectors, one of which includes the role of protein trafficking in maintaining protein quality.

Molecular Role of Chaperones

The functional specificity of a protein is dictated by its conformation and folding is driven by the interaction between the aqueous cytosol and hydrophobic amino acids incorporated into the protein. Normally, the

hydrophobic amino acids are driven into the centre of the protein to avoid the association with water and this drives the folding of the hydrophilic domains around them. A form of protein secondary structure called the β-pleated sheet is prone to aggregation due to exposed hydrophobic domains. Self-propagating aggregation is a fundamental property of ►amyloids, or aggregates of peptides that polymerize into a cross beta structure. Chaperones can prevent aggregate formation by recognizing stretches of hydrophobic amino acids that are exposed upon translation or misfolding and can initiate one of three pathways: promoting proper folding by an ATP dependent mechanism, preventing aggregation by shielding the hydrophobic domains that would normally aggregate with hydrophobic domains of other proteins or targeting misfolded proteins for degradation by recruiting ubiquitinating enzymes and subsequent degradation by the 26S proteasome (Fig. 1). The proteasome is a major component of the protein quality control system that recognizes ubiquitinated proteins that have been targeted for degradation by chaperones.

Common eukaryotic chaperones include the ►heat shock family of proteins that were originally identified as proteins upregulated in response to thermal stress but are now understood as essential components of the chaperone network in all cells. Two members of the heat shock family have particular importance in the nervous system: Hsp70 and Hsp90 [1]. Hsp70 is a chaperone that acts in a large multisubunit complex responsible for interacting with hydrophobic stretches of amino acids in nascent polypeptides to prevent the aggregation of peptides that have not completed translation, and is also required for folding the new protein [2]. Chaperones typically assist in folding by associating with exposed hydrophobic surfaces using several rounds of ATP



Chaperones: Protein Trafficking. Figure 1 Generalized chaperone function. Chaperones, particularly the Hsp70 complex, associate with hydrophobic domains of newly translated proteins off the ribosome. The Hsp70 complex can aid in the proper folding of the protein into its functional conformation. Environmental stress and exposure to toxic agents can cause denaturation of the folded protein. Depending upon the degree of damage, and the type of chaperone associated with the misfolded peptide, chaperones can prevent aggregation of misfolded intermediates, promote refolding, or target the peptide for degradation by ubiquitination and subsequent degradation by the proteasome.

dependent substrate binding and release. When the degree of unfolding is terminal, the Hsp70 complex can interact with CHIP (carboxyl-terminus of Hsp70 interacting protein) and BCL-2 associated athanogene-1 (BAG-1) that ubiquitinate the peptide to target it for degradation by the ►ubiquitin proteasome pathway (UPP) [3]. It has been found that the UPP components in particular are abundant in cytoplasm at synapse suggesting that protein degradation is a common mechanism at the neuron termini.

Hsp90 has been shown to have chaperone activity on a wide variety of client proteins and is thought to act later in the folding cascade than Hsp70. Additionally, Hsp70 and Hsp90 are often found together as a large chaperone complex that service a wide range of misfolded intermediates and act with an equally diverse array of substrate-specific co-chaperones to promote folding or refolding. Both the Hsp70 and Hsp90 complexes have been associated with neurodegenerative diseases of protein accumulation including Alzheimer's, Parkinson's and ►Huntington's diseases, suggesting that a failure of protein folding may be a primary cellular factor in determining onset of these diseases.

Because the common feature of many neurological diseases are large cellular inclusions it was thought that the aberrant aggregation caused cell death, however, the dogma is shifting to advocate that a pre-aggregated form of the affected protein oligomerizes into ►protofibrils and it is the protofibril that causes disease. How, or if, these protofibrils cause disease is unclear but it has been suggested that the cause of neuron death may be due to an effect on multiple different cellular processes including cell cycle regulation and protein quality control pathways. Aggregates not only contain the major disease specific protein but also often contain chaperones, components of the proteasomal pathway and cell cycle machinery suggesting that multiple mechanisms attempt to rectify the aggregation of toxic proteins but in turn are sequestered into the inclusion [4]. Sequestering toxic proteins may be a strategy used by the neuron to neutralize the toxic protofibrils, where cellular machinery such as the microtubule organizing centre (MTOC) are actively involved in inclusion formation. Protofibril formation may not be the sole cause of all the various neurodegenerative diseases but is likely a critical step in disease progression.

Neurodegenerative Diseases of Protein Quality

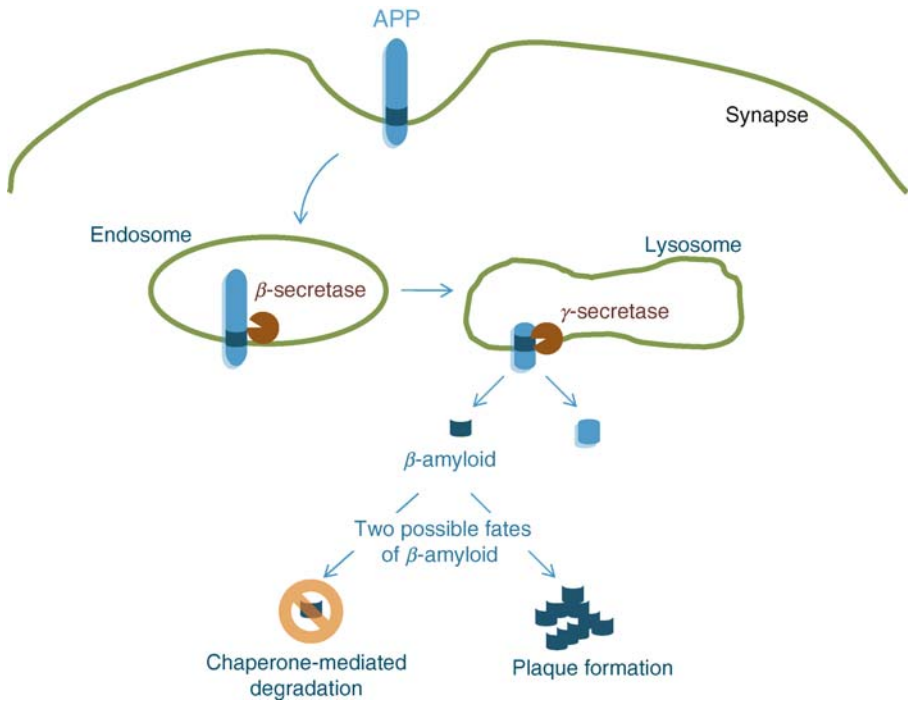
Protein aggregates are a unifying feature of a large number of neurodegenerative diseases that affect the human population (Table 1).

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease where 10% of individuals over the age of 65 will eventually develop AD and 1–2% of the same demographic will develop Parkinson's disease (PD). The diseases show diverse clinical manifestations as a result of cell death occurring in different neural subtypes in the brain where specific toxic peptides cause eventual death of those neurons and the formation of brain lesions. Alzheimer's disease, Parkinson's disease and the polyglutamine diseases represent a major class of neurodegenerative disorders that result from defects in protein folding and aberrant aggregation.

Alzheimer's Disease: AD is characterized by the formation of both intra- and extracellular protein aggregates. The extracellular plaques are composed mainly of β-amyloid whereas the intracellular neurofibrillary tangles (NFT) are composed mainly of a microtubule associate protein, tau. It has been known for some time that amyloid precursor protein (APP) is associated with AD; APP is a single pass membrane protein that is normally trafficked through the endocytic and secretory pathways (Fig. 2). Cleavage of APP

Chaperones: Protein Trafficking. Table 1 Types of aggregates in common neurodegenerative diseases

Disease	Inclusion	Abnormal Protein	Co-aggregates
Alzheimer's disease	Cytosolic neurofibrillary tangles	Tau	Ubiquitin, Hsp70, CHIP
	Extracellular amyloid plaques	β-Amyloid peptide	Hsp20,27,72 and Hsp90
Polyglutamine diseases	Nuclear and cytosolic inclusions	Huntingtin, ataxin and more	Hsp70, Hsp40, ubiquitin
Amylotrophic lateral sclerosis	Skein and Bunina bodies	Superoxide dismutase	Ubiquitin
Parkinson's disease	Lewy body	α-synuclein	Ubiquitin, proteasome, Hsp70, Hsp40
Prion disease	Extra and intracellular aggregates	PrP	Hsc70, ubiquitin



Chaperones: Protein Trafficking. Figure 2 Production of β-amyloid in the neuron. Amyloid precursor protein (APP) is a single pass transmembrane protein that is recycled via the endocytic pathway. Once in the endosome an enzyme called β-secretase can cleave APP at amino acid 671 leaving a membrane bound fragment. As the endosome enters the lysosome another secretase (γ-secretase) can cleave the sAPPβ fragment into β-amyloid. β-amyloid can be degraded by the proteasome through chaperone-mediated degradation or, if the UPS system is overloaded, may aggregate into disease causing protofibrils.

produces the disease causing peptide (β-amyloid) and this cleavage occurs during normal cell protein turnover by enzymes located in the endosomes releasing the extracellular domain. It is the location of the cleavage site that causes the formation of neutral or toxic β-amyloid. β-amyloid can be produced intracellularly during receptor recycling of cellular vesicles, and it can also occur in the ER/Golgi network prior to APP secretion, suggesting that the formation of the toxic peptide is a result of normal cell protein turnover. The reduced efficiency of vesicle movement with age or due to mutation may result in a traffic jam of cellular components in the axon; this decreased movement of vesicles may increase the susceptibility of cleaving APP into β-amyloid.

The normal production of β-amyloid suggests that chaperones, specifically the Hsp70/90 complex could be involved in preventing oligomerization and targeting β-amyloid for degradation. There is substantial evidence that induction of ►heat shock proteins provides protection from AD in mouse and cell culture models suggesting that chaperones play a role in the pathogenesis of the disease. Additionally, Hsp70 is a common component of both neurofibrillary tangles and amyloid plaques suggesting that chaperones attempt to process the toxic peptides prior to accumulating in the aggregates.

Research suggests that intracellular β-amyloid is an early event in neuronal dysfunction and there is mounting evidence that β-amyloid is the causative agent of neuronal cell death [5]. Therefore, the findings in Alzheimer's disease cellular progression represent a new way of thinking about protein folding disorders where it is the soluble form of an oligomeric peptide that causes disease and the aggregates in fact represent the cells strategy to cope with the accumulation of toxic soluble proteins.

►Huntington's and other Polyglutamine Diseases: Polyglutamine (polyQ) diseases are inherited disorders that result from an increased number of the glutamine codon (CAG) tandemly repeating in specific genes. Chaperones co-aggregate with polyQ peptides in the intranuclear inclusions suggesting that molecular chaperones are required for processing the aberrant peptides. Evidence for the role of chaperones in polyQ diseases is that overexpression of multiple different chaperones

(Hsc70, Hsp70, Hsp40 and Hsp27) all suppress the disease phenotype, but have varying effects on the formation of inclusions, suggesting a central role for chaperones in the pathogenesis of these diseases [6]. Additionally, components of the ubiquitination pathway are found in the inclusions and it has been shown that the proteasome can only hydrolyze shorter segments of polyglutamine tracts [1]. Therefore, the cause of polyglutamine diseases may be that the polyQ tracts exceed the capacity of the proteasome to degrade the toxic protein.

►Parkinson's: Parkinson's disease (PD) is diagnosed by α-synuclein aggregates that form in dopaminergic neurons of the substantia nigra in the brain causing resting tremor, muscle rigidity and reduced strength in patients. Similar to the other neurodegenerative disorders, the aggregates or Lewy bodies are not thought to be the toxic agent; α-synuclein has been found to selectively block transport between the ER and Golgi resulting in a traffic jam and accumulation of partially folded proteins in the ER. Protein accumulation results in ER stress and activation of the ERAD (►ER associated degradation) cascade to translocate proteins back into the cytosol and degrade proteins via the proteasome. The intracellular accumulation of α-synuclein protofibrils has been shown to affect multiple cell processes including induction of the ►apoptosis (or Programmed Cell Death) cascade possibly resulting from increased ER stress.

Familial Parkinson's disease (PD) can be caused by more than five different genetic loci with many of the linked genes being related to the protein quality control mechanism, including UCH-L1, Parkin and α-synuclein [7]. PD is the only neurodegenerative disease thus far that is caused by mutations in the UPP directly forming a link of protein quality control and neurodegeneration. Hsp70 and Hsp40, along with ubiquitin and components of the proteasome are found in Lewy bodies suggesting that chaperones and the UPP are essential in attempting to deal with the increased α-synuclein accumulation and get sequestered into aggregates without degrading or refolding the toxic species.

Future Directions and Therapeutics

Protofibril formation and protein misfolding are likely occurring throughout a lifetime and it may be that the loss of chaperone activity with age contributes to the late age of onset for the majority of non-inherited neurodegenerative diseases. Many unknowns still exist regarding the initial toxic agent in different neurodegenerative diseases but all potential therapeutic interventions must address the initial cause of disease progression. Chaperones provide a potential therapeutic target for dealing with the early stages of neurodegeneration because upregulation of chaperones has been shown in multiple different disease models to suppress the progression of the disease. How chaperones suppress disease progression is unknown but may act at multiple different stages including protofibril formation, prevention of fibrillar structures, promotion of protofibril refolding or degradation or promotion of amorphous aggregates. The complexity of the cellular effects of aggregation diseases indicates that simply interfering with one of the downstream effects may not prevent disease progression and neurodegeneration.

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Character Neurosis

►Personality Disorder

Characteristic Frequency

Definition

The frequency of a sound at which the response threshold of a given auditory neuron is the lowest, i.e. at which the neuronal sensitivity is highest.

►Cochlea
►Tonotopic Organization (Maps)

Characterogenic Neurosis

►Personality Disorder

Charcot-Marie-Tooth (CMT) Disease

Definition

Inherited, slowly progressing ►peripheral neuropathy appearing in early childhood and characterized by muscle weakness and wasting, reflex reductions or loss, and reduced sensation in the limbs according to a glove-and-stocking pattern. Type 1 of CMT shows ►demyelination of peripheral nerves (with reduced nerve conduction velocities) with some (at times excessive) childhood remyelination, while Type 2 does not. Both types are autosomal recessive. A severe childhood form (CMT3) is also called Severine-Sottas disease. The three different forms may be due to differences in "gene dosage" resulting from alterations of the number of alleles remaining intact after mutations. For instance, CMT1 may come about by doubling of one allele on one chromosome yielding dosage three; in CMT2, one allele on one chromosome may be dysfunctional yielding dosage one; and in CMT3, both alleles may be dysfunctional yielding dosage zero and giving rise to the severe childhood form.

►Peripheral Neuropathies

Chemesthetic Substances

Definition

Chemical compounds which activate receptors located in the oral and nasal area and mediating sensations such as pain, touch thermal, irritation (burning, cooling, stinging, tingling) through the trigeminal nerve (cranila nerve V).

Chemesthetic sensations can arise from anywhere on the body's surface since these receptors are present in skin and mucosal surfaces.

Chemical Communication

►Muscle and Tendon Energy Storage

Chemical Energy

Definition

The energy associated with the chemical state of the matter in the system.

►Energy/Energetics

Chemical Gradient

Definition

A concentration gradient reflecting gradual changes in molecule density. A chemical gradient can be generated by diffusion of soluble or volatile molecules, or by graded expression of surface-bound signals and their receptors.

Chemical Senses

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Definition

Chemical senses (►chemical sensors) are sensory organs and neural systems dedicated to the molecular detection and neural processing of environmental or biological signals.

Characteristics

Cells are "irritable": they react when exposed to chemicals. Chemical sensitivity is a property of the simplest forms of life that are endowed with chemical sensors and is also manifest in the most evolved organisms. To detect chemical signals, evolution has provided animals with specific receptor proteins distributed in the membrane of specialized sensory cells. These receptor cells are distributed in distinct chemosensory organs and systems, namely the main and accessory olfactory systems (i.e., the two ►channels of smell), the taste system and the chemoreceptive component of the trigeminal nerve. Here, the focus will be placed on major features of these chemical senses.

Chemical Signals

Chemical stimuli are molecules and ions and chemical senses are molecular senses. Molecules are transported to the contact of chemosensory cells either by air or by water. Yet, knowing the nature of the diffusion medium does not offer a sufficient criterion to classify sense organs. Even though the olfactory system detects airborne stimuli at low concentration in mammals and insects while the gustatory system detects waterborne, sapid molecules with a lower sensitivity, this is not the case for fish and aquatic crustaceans that have a true olfactory system detecting waterborne odorants with a high sensitivity [1].

Another system bringing ►chemosensory information is represented by the taste system specialized in the detection of chemical properties of potential foods and evaluation of their nutritional value. In contrast, the olfactory system has a much wider involvement in the detection of environmental and social odors. Yet, odors are also strongly involved in food intake and cooperate with taste as essential components of flavors.

Odorants emitted and sensed by individuals of the same species, for example sex attractants, are called pheromones. There are several categories of pheromones. Reproductive pheromones trigger sex recognition, courtship displays and sexual activity; in addition to these behavior-oriented functions, they also initiate long-term physiological – mainly hormonal – changes in the recipient animal. Maternal pheromones guide newborn towards mother nipples; recognition pheromones are involved in labeling the identity and social status of individuals; aggregation and dispersion pheromones maintain individual spacing. Odorants and pheromones (at least sex pheromones) were thought to be detected by two distinct sensory organs, the olfactory epithelium (OE) and the vomeronasal organ (VNO), respectively. In fact, the OE can also detect pheromones, whereas the VNO can also detect ordinary odorants.

Receptors

All animals detect odorants using seven-transmembrane domain receptors that activate G protein-based signalling cascades. In 1991, Buck and Axel [2] discovered a wide family of these G protein-coupled receptors (GPCRs) expressed in the rat OE and proposed that they were ►chemosensory receptors called odorant receptors (ORs). Subsequent molecular and bioinformatic studies confirmed the pioneer discovery and indicated that mammals, birds, fish, and amphibians have large numbers of genes for olfactory GPCRs expressed in olfactory organs. The OR repertoire contains around 1,000 genes in mouse and rat, 500–750 genes in human, and 100 genes in zebrafish and catfish. Independently expanded families of chemosensory GPCRs have a chemosensory function in invertebrate species [1].

The VNO of the accessory olfactory system expresses two families of GPCRs called V1R and V2R [3]. Some empirical evidence suggests that V1Rs bind to small airborne chemicals whereas V2Rs recognize water-soluble molecules.

In the gustatory system, two GPCR families, T1R and T2R, are involved in the detection of sapid molecules inducing sweet, bitter and umami sensations [4]. Identified proteins, T1R2 and T1R3, might compose a heterodimeric receptor to sweet tasting molecules whereas the T2R family contains around 30 different bitter receptors. Another family of GPCRs, the heterodimere T1R1/T1R3 that responds to many aminoacids in mice is especially sensible to L-glutamate and L-aspartate in humans. This receptor is therefore a good but non exclusive candidate to the role of umami taste detection.

Gustation use channel-receptors differing from GPCRs to sense salt and sour tastes [5]. For example, one of the most studied Na + taste receptor is a Na + highly selective channel known as ENaC, the amiloride sensitive epithelial sodium channel. This receptor is an oligomeric complex comprising three homologous subunits. Receptors to sour taste can be ordered in two groups: one group includes a channel-like EnaC that conducts an inward proton current when protons are available in the oral cavity. The second group comprises several H + -gated channels.

Knowledge of trigeminal chemoreception that operates in both oral and nasal cavity has benefited from recent studies on primary somatosensory neurons [6]. Studies led to discovering receptors to irritant substances like capsaicin, the active principle of chilli pepper and isothiocyanates found in mustard oil and horseradish. These receptors are members of the TRP ion channel family. Interestingly, capsaicin-sensitive nerve fibers are also activated by noxious heat. TRPV1 (also known as vanilloid receptor 1 or VR1), can be activated by both capsaicin and high temperature. Alternatively, low temperature activates a cold receptor called TRPM8 that is also sensible to menthol, a chemical eliciting a sensation of cold.

Receptor Evolution

The size of the OR gene superfamily varies considerably among species. Duplications have greatly increased the number of genes but deletions and inactivating mutations resulting in a large number of *pseudogenes* contributed to reduce the size of the functional repertoire [7]. The proportion of intact OR genes and pseudogenes is also quite variable. For example, the human genome contains less than 400 functional OR genes and over 400 OR pseudogenes. This decline of the OR gene repertoire is already visible, even though less marked, in apes and Old World monkeys, coinciding with the acquisition of a full trichromatic vision, which may indicate that

improving visual abilities made olfaction redundant in some its adaptive functions.

Considerable variations in gene repertoire are also observed for VNO receptors, V1R and V2R. The differences in number of V1R and V2R functional genes among vertebrates seem to point to an asymmetric evolution followed by the two gene families [8]. Only very few intact VR1 genes are found in fishes whereas the mouse and rat have over 100 genes. In contrast, the V2R repertoire is virtually lost or severely reduced in many terrestrial vertebrates (in the cow, dog and primates, including humans), but not in the opossum and rodents that have a wide V2R gene repertoire. The existence of a functional vomeronasal organ in adult humans is highly questionable.

Transduction Pathways

Olfactory neurons use two main intracellular signalling pathways utilizing cyclic nucleotides and phosphoinositide-derived signals. Cyclic nucleotide signalling is common in vertebrates and is thought to operate in nematodes (*Caenorhabditis elegans*) and arthropods [1]. Cyclic nucleotides target the olfactory cyclic nucleotide-gated ion channel through which calcium enters the cell and secondarily activates a chloride current. When activated, ion channels generate a graded voltage response that triggers action potentials. In crustaceans, olfactory receptors seem to use phosphoinositide signalling, whose target is a presumptive homolog of the TRP family of ion channels. Phosphoinositide signalling has been implicated in some way in olfactory transduction in other, phylogenetically diverse species, including nematodes, insects, fish and mammals.

Taste transduction is complex [5]. Bitter taste detection involves the taste- specific signalling G protein, gustducin. Two transduction pathways are simultaneously activated by receptors of the T2R family: receptor activation triggers a transient decrease in cAMP and cGMP, along with a transient increase in IP3. Like bitter- taste transduction, sweet-taste transduction has cyclic nucleotides and IP3 as intracellular messengers. Sugars and artificial sweeteners are supposed to use distinct pathways.

Sensory Organs and Pathways

The peripheral organization of sensory pathways differs notably between the main and accessory olfactory systems, on the one hand, and the taste system, on the other hand. Several common features can be observed in olfactory systems of vertebrates and arthropods. In most animals, the primary olfactory afferents that are axons of receptor neurons, project to the CNS without intermediate synapsing. The first synaptic relay, that is the olfactory bulb in mammals, antennal lobe in insects and olfactory lobe in crustaceans, is similarly organized in arthropods and mammals. The olfactory afferents converge into the dense neuropile of glomeruli where they terminate on both projection neurons and local interneurons. In mammals, this projection is narrowly selective: all receptor neurons expressing the same type of OR converge onto one or two glomeruli. In turn, each projection neuron connects one or a few glomeruli to the primary olfactory cortex in mammals and the lateral protocerebron and corpora pedunculata in arthropods.

A similar organization pattern is shown by the accessory olfactory system. VNO receptor cells that are neurons project to glomeruli in the accessory olfactory bulb (AOB) located in the caudal part of the main OB. In those mammals that have both V1R- and V2R-expressing sensory neurons (rodents, opossum), the two populations separately project their axons to segregated (anterior and posterior) regions of the AOB. In all other examined mammals that have VNO, the projection system is uniform. Then, relay neurons directly project to the hypothalamus.

Gustatory receptor cells are grouped in taste buds inside three types of taste papillae. The spatial distribution of the different taste receptors in the tongue and the mouth is not homogenous but expression zones of different receptors overlap to some extent. Differing from olfactory sensory cells, taste cells have an epithelial origin, they are not neurons. The apical portion of a taste cell possesses fine expansions, called microvilli, equipped with taste receptors. Receptor activation by sapid molecules triggers ionic currents generating action potentials that are synaptically transmitted to fibers of the gustatory nerves (cranial nerves VII, IX, X). A single afferent fiber makes synapses with several taste cells. Taste afferents project to the rostral part of the Nucleus Tractus Solitarius (NTS) in the brain stem.

Neural Coding

Chemical senses have the function of allowing animals to identify substances, objects, places or living beings on the basis of their molecular properties that induce sensations endowed with specific qualities. Understanding how the molecular identity of an odor or a taste is coded in corresponding sensory organs and pathways is a fundamental question. Some common principles and notable differences can be found between olfaction and taste. In the olfactory system it is generally agreed that each cell expresses a single type of OR, individual receptor cells can be activated by different odorants and individual odorants activate multiple receptor cells [9]. These properties give support to the concept of combinatorial coding [9] that is valid in both vertebrates and insects: an odor is represented as a specific combination of excited neurons that reproduces the specific combination of activated ORs. The other possible coding strategy consisting in dedicating neurons to the detection of a particular odorant ("labeled lines" coding), seems to be exceptional (lobster). Recent

studies suggest that the discriminative capacity of the static combinatorial coding could be improved in projection neurons by including a temporal dimension.

There is less agreement regarding the coding of taste qualities [10]. Like in the olfactory system, in the taste system individual afferent fibers respond to multiple stimuli and even to stimuli representing different "basic" qualities: i.e., NaCl, HCl, sucrose, quinine. This can be explained because individual afferent fibers innervate several taste cells and taste cells individually display multiple chemical sensitivities. A combinatorial coding, originally called "across-fiber pattern" [10] coding could therefore operate in the taste system. However, the taste system differs from the olfactory system in that a limited number of taste qualities can be recognized in the former, whereas qualities cannot be consensually classified in the latter. A solution was proposed once to conciliate apparently opposite views: among several stimuli inducing responses from a taste afferent, one would be more efficient than every other; afferents could thus be grouped according to their "best" stimuli. This proposal failed to close the debate. Whether neural activity data support the view that taste qualities form a continuum or are more in favor of the traditional "four basic taste" theory is still a matter of individual belief. Falsification of either model seems to be difficult or impossible. Hopefully, unrevealing mechanisms of taste reception does not require previous solving of the conceptual puzzle.

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Chemical Sensor

Definition

A type of detector that is sensible and reacts to molecular properties of chemical compounds.

►Chemical Senses

Chemical Synapse

Definition

Specific junction of contact between nerve cells and their targets allowing transmission of chemical signals from the nerve cell to target cells.

►Synaptic Transmission: Model Systems

Chemical Transmitter

►Neurotransmitter

Chemokines

Definition

Chemokines are families of cytokines that induce directed chemotaxis in nearby responsive cells, hence the name chemotactic cytokines. Chemokines are small secreted proteins, produced by many different cell types, which function in both physiological and pathological conditions. These proteins signal effector cells through cell surface binding to seven transmembrane domain G-protein coupled receptors. At least 50 different chemokines have been identified. Chemokines are best characterized as chemoattractants for immune cells and glia. However, certain chemokines also have antimicrobial activity, angiostatic activity, can stimulate cell proliferation and are neurotrophic.

►Chemotaxis
►Cytokines

Chemoreceptor

Definition

Chemoreceptors are receptors which are sensitive to changes in chemical substances or gas tension. The peripheral chemoreceptors are in the carotid artery bifurcation (carotid bodies) and arch of the aorta (aortic bodies). They are sensitive to changes in oxygen and carbon dioxide tension and hydrogen ion concentration in the blood. Central chemoreceptors located in the brain are sensitive to hydrogen ion concentration of the cerebrospinal fluid. The chemical to which a chemoreceptor is sensitive may bind receptors on the cell surface or affect cellular processes such that the ionic currents across the cell membrane are differentially affected, thereby affecting membrane potential and altering the spiking activity of the cells. The ambient abundance of the chemical substance to which the chemoreceptor is sensitive can therefore be encoded by the amount of spiking activity of the cells comprising the chemoreceptor.

►Central Chemoreception
►Central Nervous Chemoreceptors and Respiratory Drive
►Homeostasis

Chemosensation

Definition

Identification of chemical compounds encountered by the organisms. Mediated by cells specialized for detection and transformation of information into electrical signal.

►Olfactory Sense

Chemosensory Information

Definition

Information generated by biological chemical sensors and transmitted in sensory pathways; the olfactory system and the taste system transmit and process chemosensory information.

►Chemical Senses
►Gustation
►Olfactory Sense

Chemosensory Receptor

Definition

A type of chemical sensor or detector of biological origin that equips a chemosensory system; a G protein-coupled receptor (GPCR) is a chemoreceptor.

►Chemical Senses

Chemotactic Attractant

Definition

Chemotactic attractants are chemical molecules that induce motile behavior towards the source of the attractant (positive chemotaxis). This behavior occurs at all levels of biological organisation, from single-cell organisms such as bacteria to eukaryotic cells, organs and entire multicellular organisms. In contrast, chemotactic repellents induce the adverse migratory effect (negative chemotaxis). Chemotaxis is a receptor-mediated process and dependent on concentration gradients of chemical cues.

Classical examples for chemotactic behavior are bacteria detecting glucose as food source; the aquatic protozoon tetrahymena shows chemo-attraction for the amino acids glycine, proline, and glutamine, while tyrosine and phenylalanine act repulsive; the eukaryotic amoeba dictyostelium discoideum expresses cyclic AMP receptors; semaphorins represent negative axon guidance molecules; together with the olfactory and taste receptors, most receptors underlying chemotaxis of eukaryotic cells belong to the superfamily of G protein- coupled receptors (GPCRs).

Recently, an odor receptor that functions in chemotaxis of human sperm has been identified and may represent a critical component of oocyte fertilization. Stimulation of sperm with the aldehyde burgeonal, which is perceived as “lily of the valley” by the human nose, increases chemotaxis behavior of sperm, while the aldehyde undecanal appears to act as competitive antagonist on sperm navigation.

►Cyclic AMP
►G Protein-Coupled Receptor (Metabotropic Receptor)
►G-Protein Coupled Receptors (GPCRs) in Sensory Neuron Function and Pain
►G-protein Coupled Receptors (GPCRs): Key Players in the Detection of Sensory and Cell-Cell Communication Messages
►Olfactory Receptor
►Semaphorin
►Taste

Chemotaxis

Definition

Cell movement in response to a concentration gradient of a specific chemical.

►Chemotactic Attractant

Chemotopic Representation

Definition

A chemotopic representation indicates an orderly spatial arrangement of olfactory glomeruli (or other neural elements in a chemosensory system) that is related to the chemical attributes of the effective sensory stimuli. In the rodent olfactory bulb, chemotopic organization involves the spatial clustering of glomeruli responding to odorant chemicals with similar functional groups, hydrocarbon structures, or overall molecular properties such as water solubility. A further chemotopic organization is present in some glomerular modules of the rat bulb, wherein glomeruli responding to aliphatic odorants of increasing length are located in progressively ventral glomeruli.

►Glomerular Map
►Olfactory Bulb
►Olfactory Sense

Chewing

►Mastication

Cheyne-Stokes Breathing

Definition

Disturbed pattern of breathing in ►coma patients with diffuse forebrain damage but without brainstem injury, characterized by increasing and decreasing depth of respiration and interposed apneas.

►Coma

Chinese Room Argument

Definition

This thought experiment, conceived of by John Searle, is intended to show that computers are not capable of understanding, or in other words, that implementing a computer program defined in terms of the manipulation of formal symbols, or syntax, is not sufficient for semantics. Searle, a non-Chinese speaker, imagines himself inside a room performing counterparts to all of the relevant operations that a computer running a program designed to respond in Chinese to Chinese questions would perform. For example, when a card comes in trough a slot in the box with a question, (the input), he consults a rule book (the program), which tells him which cards with Chinese symbols he should side out of the slot (the output). Searle argues that though his output could be mistaken for that of a native Chinese speaker, the process of performing these operations according to the rule book provides him with no understanding of Chinese. Since, he argues, there is no significant difference between what he does inside of the room and what a computer does, he concludes that the computer does not understand Chinese either.

►Physicalism

ChIP

►Chromatin Immunoprecipitation and the Study of Gene Regulation in the Nervous System

Chitosan

Definition

Chitosan is the de-acylated derivative of chitin, a polysaccharide extracted from crustacean exoskeletons or generated via fungal fermentation processes. Chitosan is a beta-1,4-linked polymer of 2-amino-2-deoxyd-glucose. It carries a positive charge from amine groups.

►Transplantation o Artificial Materials for Nerve Regeneration

CHL1

Definition

One type of L1, immunoglobulin superfamily.

►Regeneration of Optic Nerve

Chloride Channels (ClC)

Definition

Chloride (ClC) channels are ion channels which bear a high selectivity for inorganic anions, principally, chloride ions. Chloride channel gates open in response to depolarization, but their voltage-sensing capabilities are weaker than the voltage-gated ion channels such as potassium, sodium or calcium channels. Chloride channels contribute to the negative resting membrane potential in skeletal muscle, and have critical physiological roles in regulation of cell volume and pH.

►Chloride Channels and Transporters

Chloride Channels and Transporters

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Definition

Chloride (Cl^-) channels and transporters are ►integral membrane proteins that function to allow Cl^- and other inorganic anions to cross the ►cell membrane (►Cell membrane – components and functions). Chloride channels act by forming a continuous aqueous pore across the membrane that allows Cl^- ion to move passively down its electrochemical gradient. Chloride transporters, on the other hand, link Cl^- movement across the membrane to that of another ion thereby allowing, in some situations, Cl^- to diffuse *against* its electrochemical gradient (►Ion transport).

Characteristics

Introduction

Chloride is a unique ion in the cellular physiology of the nervous system. Whereas the electrically important inorganic cations (Na^+, K^+, Ca^{2+}) are maintained with strong, predictable gradients across neuronal membranes (►Membrane potential – basics), Cl^- anion gradients are variable, tailored to the physiological role of this anion in a given cell type at a given developmental stage. In some cells, Cl^- is passively distributed, adjusting its gradient according to the ►resting membrane potential of the cell. Activation of Cl^- conductances in those cells cannot therefore change the membrane potential; it can, however, attenuate ►electrical excitability by reducing the ►membrane resistance. In other neurons, Cl^- concentrations are more tightly controlled, being either actively extruded or accumulated. The resulting shift in the Cl^- ►equilibrium potential, by controlling whether activation of Cl^- channels is inhibitory or excitatory, has a major effect on excitability in the central nervous system (CNS). This effect can be dynamic, as in the ►suprachiasmatic nucleus, where there is a daily oscillation in the neuronal response to ►$GABA_A$ receptor activation, or it can be developmentally regulated, as in ►synapses containing $GABA_A$ receptor Cl^- channels which switch during development from excitatory to inhibitory [1]. (For further information see essays on ►Chloride homeostasis and development and ►Ion transport).

Chloride conductances serve a wide range of physiological roles in the nervous system. These functions result not only from channel activity but also from the working of a series of transporters that move Cl^-, both passively and actively. Perhaps the most thoroughly studied neuronal Cl^- channel is the ►$GABA_A$ receptor, a member of the cys-loop family of ►neurotransmitter-activated (►ligand-gated) channels. As this protein is covered thoroughly in other articles, we will focus here on other Cl^--transport mechanisms. These other pathways fall into two broad categories: some have been identified at a molecular level, offering the possibility of genetic (and other) manipulations; others have been described only in terms of their functional behavior, observed in ►patch clamp recordings of neuronal cells but not yet cloned.

Molecularly Identified Cl Conductances

CLCs

The CLC "Cl^- channel" family is a broad molecular family with diverse neurological functions. The family is unique in that it contains both types of Cl^--transport proteins, channels and transporters. The family members that are channels reside on the ►plasma membranes of cells, while the transporters reside on intracellular membranes.

The high-resolution structure of a prokaryotic CLC family member, a transporter from *E. coli*, has been solved [2]. The protein is a two-subunit homodimer, with separate and independent Cl^- permeation pathways housed within each subunit. The proton permeation pathway is less well defined, but is thought to be coincident with the Cl^--permeation pathway at the extracellular entrance to the protein, and to diverge at the intracellular end. Both CLC channels and CLC ►antiporters are thought to share this same basic architecture.

CLC Channels [3]

ClC-1

ClC-1 is a ►depolarization-activated Cl^- channel that resides in the plasma membrane of ►skeletal muscle cells and is crucial for the rapid recovery of the ►membrane potential between ►action potentials. Skeletal muscle cells receive input from ►motor neurons, which leads to the opening of ►voltage-gated Na^+ channels and results in membrane depolarization. Subsequent movement of Cl^- through the depolarization-activated ClC-1 channels facilitates ►repolarization of the membrane to allow continued electrical excitability. In addition to being activated by depolarization, ClC-1 ►open probability is also activated by intracellular pH and by extracellular Cl^-. Defects in ClC-1 lead to ►myotonia congenita, a disease in which the skeletal muscle repolarization is delayed, thus causing trouble with movement. Over 60 different mutations that cause this disease are known.

ClC-2

ClC-2, like ClC-1, is voltage-, Cl^-- and pH-dependent; however, it is activated by ►hyperpolarization rather than by depolarization of the membrane. ClC-2 is expressed broadly in the nervous system. It may play a role in controlling neuronal excitability by determining whether GABA responses are excitatory or inhibitory, as discussed above. ClC-2 is also broadly important for Cl^- ion ►homeostasis in the CNS. A ClC-2 knockout mouse has ►retinal degeneration and ►leukoencephalopathy. In humans, mutations in ClC-2 have been reported to cause some forms of ►absence epilepsy.

ClC-K

The two ClC-K channels (Ka and Kb) lack significant voltage dependence. This is consistent with their role in transepithelial transport (►Ion transport). They are also regulated by extracellular Ca^{2+} and H^+, though the pH dependence is the opposite to that found in ClC-1 and ClC-2. Although the CLCKs are predominantly expressed in the kidney, they are also found in the ►cochlea (►organ of Corti, ►spiral ligament, and ►stria vascularis), where they contribute to the ion homeostasis essential for cochlear function. Unlike ClC-1, which appears to act independently, the ClC-K proteins require an accessory subunit, Barttin. (It is not yet known whether ClC-2 has any accessory subunits.) Mutations in Barttin cause deafness in humans.

CLC antiporters [4]

Two of the three subfamilies of mammalian CLC proteins are comprised of Cl^-/H^+ antiporters (ClC-3/4/5 and ClC-6/7). These proteins are primarily targeted to intracellular organelles where they seem to play roles in organellar acidification. Knocking out the genes for these proteins leads to a range of defects, with several having important repercussions for the CNS.

ClC-3

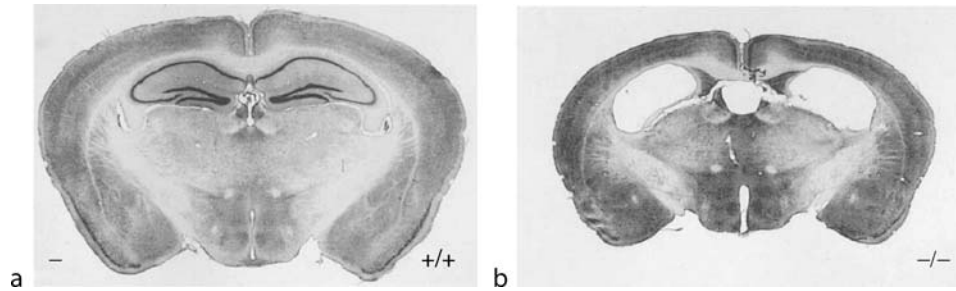
ClC-3 is a protein with a controversial history. At one time ClC-3 was proposed to be a volume-regulated Cl^- channel, but this is no longer considered likely, as ClC-3 knockout mice display normal volume-regulated Cl^- currents. Knocking out ClC-3 has profound results in the CNS; ClC-3 knockout mice show severe CNS degeneration with specific loss of the ►hippocampus by 3 months postnatal (Fig. 1). ClC-3 was suggested to play a role in neurotransmitter transport vesicles as it is primarily localized to these compartments. A recent publication proposed a competing view of ClC-3 in the CNS, with it functioning as a ►CAMKII-regulated Cl^- channel that can modulate the efficacy of ►synaptic transmission.

ClC-4/ClC-5

ClC-4 and ClC-5 are generally agreed to localize to intracellular compartments; both were recently demonstrated to act as Cl^-/H^+ antiporters. Though disease phenotypes resulting from ClC-5 primarily manifest in the kidney, this protein is also highly expressed in the brain. ClC-4 which has high (>75%) sequence identity with ClC-5 (and with ClC-3) is expressed at high levels in brain and several other organs. Though neither of these has been studied in the CNS, in other tissues they have been shown to be important for the acidification of endosomes early in the endocytic pathway and they probably subserve similar roles in the brain.

ClC-6/ClC-7

The third ClC subfamily, consisting of ClC-6 and ClC-7, are localized to late endosomes (ClC-6) and lysosomes (ClC-7) where, similarly to ClC-5, they may be important for allowing the acidification by shunting the voltage generated by the ►vacuolar H^+-ATPase. Both proteins are prominently expressed in brain as well as other organs, and for both proteins knockout experiments indicate roles in CNS physiology. For ClC-6 the major phenotype in the knockout is impaired ►nociception and mild behavioral abnormalities; these apparently result from a ►lysosomal storage disease



Chloride Channels and Transporters. Figure 1 CNS effects of knocking out the ClC-3 Cl^- transporter. Frontal sections of brains from wildtype (*left*) and ClC-3 knockout (*right*) mice (7 months old) are shown, revealing the prominent absence of the hippocampus in the knockout mouse. The hippocampus is present at birth in the knockout mice, but gradually degenerates starting at about 3 months of age and is replaced by a large cavity communicating with the ventricular system. These mice also suffer from retinal degeneration. Reprinted from *Neuron,* 29, S. M. Stobrawa et al. Disruption of ClC-3, a Cl^- channel expressed on synaptic vesicles, leads to a loss of the hippocampus, pp 185–196 (2001), with permission from Elsevier.

that resembles human neuronal ceroid lipofuscinosis. The phenotypes of ClC-7 knockouts are consistent with its broader expression: in both affected humans and knockout mice, loss of ClC-7 leads most prominently to osteopetrosis, the hypercalcification of the bone matrix. Additionally, these individuals also suffer from retinal degeneration as well as a severe lysosomal storage disease, which again resembles neuronal ceroid lipofuscinosis. Targeting of ClC-7 to lysosomes requires the presence of a recently-reported β-subunit, Ostm1, whose knockout causes a similar disease spectrum to that of disrupting ClC-7 itself.

Bestrophin [5]

►Best disease is an inherited form of ►macular degeneration wherein accumulation of retinal metabolites leads to retinal cell death and blindness. Features of the electroretinogram in Best disease patients suggest involvement of a Cl^- conductance in the basolateral membrane in the ►retinal pigment epithelium. Furthermore, ►Bestrophin, the protein affected in Best disease, has been shown to function as a ►Ca^{2+}-activated Cl^- channel (below) when expressed in heterologous systems. It remains unclear whether Bestrophin is responsible for Ca^{2+}-activated Cl^- conductances in other tissues.

Neurotransmitter Transporter Anion Conductances [6]

In addition to those proteins whose primary purpose is to transport Cl^-, a variety of neurotransmitter transporters carry associated Cl^- conductances. Both the ►dopamine and ►glutamate transporters, responsible for clearing synapses of these neurotransmitters, show such conductances. Different glutamate transporters have different relative capacities for Cl^- flux versus glutamate transport, with some showing significantly higher Cl^- currents than transport-associated currents. These Cl^- currents recently have been shown to contribute to the communication between rod bipolar cells in the retina. Similarly, anion currents through dopamine transporters have been shown to modulate excitability in ►midbrain dopaminergic neurons.

Chloride Conductances Not Yet Molecularly Identified

Volume-sensing Channels [7]

Changes in osmolarity, either in the extracellular fluid or in a cell's own cytoplasm, lead to osmotically-induced movements of water which can, in turn, cause cell swelling or shrinkage. Such changes can result pathologically from changes in serum osmolarity (as a result from congestive heart failure or diabetes, for example) or from changes in cellular osmolarity (as a result from ►hypoxia or metabolic disturbances). To respond to these changes and return to normal cell volume, neurons and other cells activate a class of anion channels termed ►VRAC (for ►Volume-Regulated Anion Conductance; many other terms have been used, see [8]). These channels open in response to cellular volume changes and are instrumental in returning to normal cell volume. Though these currents have been described in a wide range of cell types, a particularly well-examined group is expressed in ►gliomas, a type of CNS cancer. These glioma Cl^- channels have been proposed to play roles in the changes in cell volume required for tumor cells to invade the densely-packed surrounding tissue.

Ca^{2+} Activated Cl Channels [8,9]

Although ►Ca^{2+}-activated Cl^- channels (►CaCCs) are physiologically widespread, the molecular identity of these channels remains controversial and the precise function of these channels is not fully understood. The best described function of the Ca^{2+}-activated Cl^- channels is in ►olfactory receptor neurons. Binding of ►odorants to these neurons results in membrane depolarization and elevation of intracellular Ca^{2+}. This rise in Ca^{2+} activates the CaCCs, which causes an efflux

of Cl^- and further membrane depolarization. This depolarization provides a critical amplification of the signal and thus enhances sensitivity to odorants. In ▶taste receptor cells, activation of CaCCs occurs similarly; however, in this case the activation produces a hyperpolarization of the cells (because the reversal potential of Cl^- in these cells is quite negative). The hyperpolarization may play a role in taste adaptation.

CaCCs are additionally expressed in many types of neurons, where they may modulate excitability by facilitating action-potential repolarization, generating after-polarizations, and inducing membrane oscillatory behavior.

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Chloride Homeostasis and Development

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Synonyms

GABA switch; Chloride switch; Excitatory GABA

Definition

The regulation of intracellular chloride ($[Cl^-]_i$) during nervous system development determines the polarity of GABAergic and glycinergic synaptic transmission. In embryonic development, the Na^+ -K^+ -$2Cl^-$ (▶NKCC1) cotransporter maintains a high concentration of neuronal $[Cl^-]_i$, rendering GABAergic and glycinergic synaptic transmission excitatory. At this stage, excitatory GABA and glycine act as trophic regulators of progenitor proliferation, neuronal migration, neurite growth, and synapse formation. During postnatal development there is an extrusion of $[Cl^-]_i$ by the neuron specific K^+ -Cl^- (▶KCC2) cotransporter, which renders GABA and glycinergic synaptic transmission inhibitory. In the mature CNS, the strength of inhibitory GABAergic and glycinergic synaptic transmission can be altered by both physiological levels of neuronal activity and by pathological events, through a KCC2-mediated regulation of Cl^--homeostasis.

Characteristics

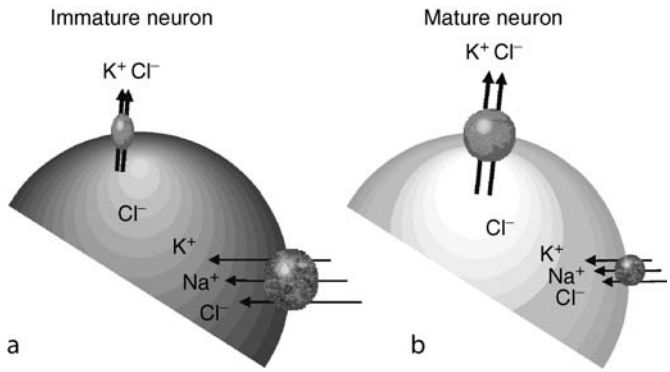
Neurons Regulate Chloride Homeostasis

Chloride (Cl^-) is the most abundant permeant anion in cells. In many non-neuronal cells, active transport does not maintain a Cl^- gradient across the neuronal membrane. The resulting passive distribution of this ion establishes an equilibrium potential for Cl^- (E_{Cl}) which is equal to the resting membrane potential (Vr). E_{Cl} is the membrane voltage at which there is no net flow of Cl^- across the membrane. Unlike non-neuronal cells, neurons express ▶cation-chloride cotransporters (CCC) which precisely regulate Cl^- homeostasis throughout development and in the mature CNS [1–3]. Electroneutral cotransport of Cl^- and K^+ and/or Na^+ is mediated by members of the CCC gene family SLC12 (solute carrier family 12) [4]. The CCCs are all secondarily active cotransporters that utilize energy from extrusion of ion(s) down their electrochemical gradient(s) in order to fuel the transport of other ions against their electrochemical gradient(s).

Neuronal Cl^- Homeostasis is Maintained by NKCC1 and KCC2

The Na^+ -K^+ -$2Cl^-$ (NKCC1) is a ~1,280 amino acid protein SLC12 gene family member, which is widely expressed in both epithelial and nonepithelial cells, including neurons and glia [4]. Early in development there is a high neuronal expression of NKCC1, which produces an influx of Na^+, K^+, and Cl^- (Fig. 1).

NKCC1 derives energy from the inward Na^+ electrochemical gradient to uptake Cl^-; the Na^+ gradient is generated and maintained by the Na^+ -K^+ -ATPase. Neuronal NKCC1 expression is maximal in the embryonic period, with a significant decrease in expression during early postnatal development. While NKCC1 mutations do not result in any known disease states, knockout mice develop deficiencies in inner ear function, endolymph secretion, sensory perception, and fertility.



Chloride Homeostasis and Development. Figure 1 The balance of CCCs determines $[Cl^-]_i$ during development. (a) NKCC1 is the dominantly expressed CCC in immature neurons. This inward transport of Cl^- results in a relatively high $[Cl^-]_i$. (b) In mature neurons, the developmental up-regulation of KCC2, coupled with decreased NKCC1 expression, produces a net Cl^- extrusion which maintains a low $[Cl^-]_i$.

During postnatal life, when NKCC1 expression is decreasing, there is a gradual up-regulation of the ~140 kDa K^+ -Cl^- cotransporter KCC2 [1,4,5] (Fig. 1). There are four K^+ -Cl^- cotransporters in the SLC12 gene family: KCC1, KCC2, KCC3, and KCC4; of these only KCC2 is neuron-specific. KCC2 is widely expressed throughout the CNS, with high expression in hippocampal pyramidal neurons, granule cells and Purkinje neurons of the cerebellum, and retinal neurons. KCC2 utilizes energy from the K^+ gradient, which is established by the Na^+ -K^+ -ATPase, to transport Cl^- against its electrochemical gradient. For every K^+ ion that leaves the neuron, one Cl^- ion enters. KCC2 is unique among the KCCs because it operates under isotonic conditions, while the other KCCs are strongly activated by cell swelling. KCC2 also has a higher cation affinity than the other KCCs, making it suited to serve as a buffer for external K^+ $[K^+]_o$. When $[K^+]_o$ is increased to 10–12 mM, which may result from increased neuronal activity, KCC2 cotransport can be reversed.

Together, decreased NKCC1 and increased KCC2 expression lead to a shift in the Cl^- electrochemical gradient during early postnatal life, resulting in a low neuronal $[Cl^-]_i$. While there is variation in the time line of this shift, both among brain structures within a species, and across species, it has been observed in nearly all brain structures and organisms examined [2].

Chloride Homeostasis Determines the Polarity and Magnitude of GABAergic and Glycinergic Synaptic Transmission

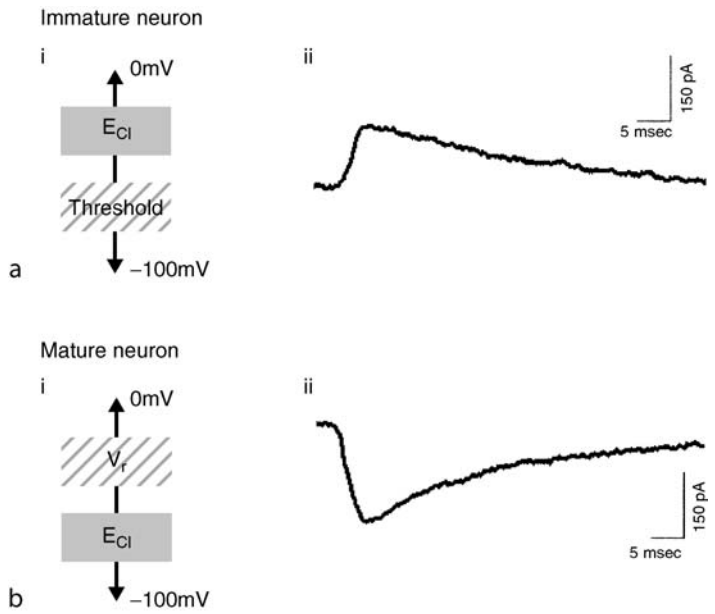
The neurotransmitters GABA and glycine both bind to ionotropic receptors (GABAARs and glycineRs, respectively) which are permeable to Cl^-. Early in development the dominant expression of NKCC1 maintains a high $[Cl^-]_i$ which maintains E_{Cl} more depolarized than the action potential threshold. Under these circumstances GABAergic and glycinergic synaptic transmission can produce action potential firing, and thus their actions are excitatory [2] (Fig. 2).

When KCC2 expression dominates in the mature nervous system, neuronal $[Cl^-]_i$ is low, which maintains E_{Cl} more hyperpolarized than the action potential threshold, rendering GABAergic and glycinergic synaptic transmission inhibitory [1,5].

What regulates the Cl^--mediated switch from excitation to inhibition is an open question [3]. *In vitro*, when GABAergic transmission was blocked during development, there was a decreased up-regulation of KCC2 expression. Similarly, *in vivo*, blocking the GABAergic transmission during development prevented the developmental up-regulation of KCC2. These results are in direct contrast with two other studies which demonstrated that chronically antagonizing GABAARs had no effect on the normal developmental time course of KCC2 up-regulation.

Trophic Roles of Excitatory GABA & Glycine

GABA is present and functional prior to the development of synaptic, where it has been shown *in vivo* to exert trophic functions during neuronal development. Premature lowering of $[Cl^-]_i$ in a subpopulation of ventricular neural progenitors, by *in utero* electroporation of KCC2, eliminated the tonic excitatory actions of GABA [3]. This resulted in a severe impairment of the morphological maturation of those newly born neurons. In addition to the role of excitatory GABA on neurite morphology, excitatory GABA also plays a critical role in the establishment of excitatory and inhibitory inputs within neuronal circuits. When KCC2 was prematurely expressed in immature tectal cells of the *Xenopus* tadpole tectum, there was increased GABAergic synaptic input to tectal neurons, while the normal developmental increase in AMPA receptor-mediated transmission was blocked [6].



Chloride Homeostasis and Development. Figure 2 E_{Cl} Determines the polarity of GABAergic and glycinergic synaptic transmission. (ai) In immature neurons E_{Cl} is more depolarized than the action potential threshold rendering GABAergic and glycinergic synaptic transmission excitatory. (aii) Under such conditions inward GABAergic currents are recorded electrophysiologically. (bi) In mature neurons, when E_{Cl} is more hyperpolarized than V_r, GABAergic and glycinergic synaptic transmission is inhibitory, producing outward currents (bii).

Early excitatory glycinergic signaling also exerts trophic functions which are required for proper nervous system development. Early excitatory glycinergic signaling was perturbed in the ►zebrafish using ►morpholino oligonucleotides (morpholinos) [7]. The resulting knockdown of the glycine receptor α_2-subunit produced ►morphants with disrupted interneuron differentiation. This decrease in excitatory glycinergic signaling resulted in a reduction in the frequency of spontaneous glycinergic and glutamatergic synaptic transmission.

The excitatory trophic actions of GABAergic and glycinergic signaling are not restricted to development. In the dentate gyrus of the hippocampus, where neurogenesis continues into adulthood, excitatory GABA regulates neurogenesis, morphological maturation, and synapse formation. In particular, when NKCC1 expression is reduced and GABA's actions are converted from excitatory to inhibitory, the dendritic development of newly generated granule cells is impaired [8].

Many of the excitatory actions of GABA and glycine are likely mediated by receptor-induced membrane depolarization, which regulates Ca^{2+} influx through both voltage-gated channels and neurotransmitter receptors. Membrane depolarization which triggers action potentials, will in turn activate voltage-gated calcium channels (VGCCs) allowing significant Ca^{2+} influx. In addition, membrane depolarization may be sufficient to remove the Mg^{2+} block from the Ca^{2+} -permeable NMDA receptor. The VGCC- and/or NMDA-dependent rise in $[Ca^{2+}]_i$ may then trigger Ca^{2+} -dependent signaling cascades responsible for developmental processes such as progenitor proliferation, neuronal migration, neurite growth, and synapse formation.

Regulation of Cl^- Homeostasis by Pain & Epileptic Activity

Peripheral nerve injury can lead to neuropathic pain, which results from hyperexcitability of dorsal horn neurons in the spinal cord. Nerve injury leads to an increased synthesis and activation of the ATP receptor on microglia. Recently, it was shown that ATP stimulates brain-derived neurotrophic factor (BDNF) release from microglia, which acts via the TrkB receptor to depolarize E_{Cl} in spinal lamina I neurons [9]. The depolarization of E_{Cl} was significant enough to convert GABAergic and glycinergic synaptic transmission from inhibitory to excitatory. A link between neurotrophic factors and Cl^- homeostasis has also been demonstrated in the hippocampus. Following epileptic seizure activity there is a BDNF-induced decrease in KCC2 expression [10].

Activity-Dependent Regulation of Cl^- Homeostasis

In the mature CNS, when GABAergic synaptic transmission is inhibitory, physiological patterns of neuronal activity can regulate the strength of inhibition [3]. When hippocampal GABAergic synapses are

repetitively stimulated with spike-timing induction protocols or when the postsynaptic neuron is stimulated alone, there is a Ca^{2+} -dependent decrease in KCC2 function. This activity-induced regulation of KCC2 leads to an increase in neuronal $[Cl^-]_i$ which depolarizes E_{Cl} Because E_{Cl} determines the strength of inhibition, the activity-dependent increase in $[Cl^-]_i$ decreases the effectiveness of inhibition. Inhibitors of Ca^{2+} -dependent protein kinase C (PKC) abolished the postsynaptic spiking induced E_{Cl} shift, whereas activation of protein tyrosine kinases or phosphatases were not required, suggesting that Ca^{2+} may act via a PKC-dependent pathway to regulate KCC2. The postsynaptic spiking-induced and spike-timing induced down-regulation of KCC2 activity occurred within minutes, suggesting an alteration in membrane trafficking, and/or posttranslational modification of KCC2, as opposed to changes in gene transcription or protein synthesis.

Conclusions

NKCC1- and KCC2-mediated Cl^- homeostasis determine the polarity and strength of GABAergic and glycinergic synaptic. Early in development when $[Cl^-]_i$ is high, excitatory GABAergic and glycinergic synaptic transmission play important roles in progenitor proliferation, neuronal migration, neurite growth, and synapse formation. In the mature nervous systems when $[Cl^-]_i$ is low, both physiologically- and pathologically-induced neuronal activity can alter Cl^- homeostasis via a regulation of KCC2, which effectively weakens the strength of inhibition.

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Chloride Switch

►Chloride Homeostasis and Development

Cholecystokinin

Definition

Cholecystokinin (CCK) is a peptide intestinal hormone that is released in response to food entering the intestine, and causes contractions of the gall bladder and secretion of enzymes from the pancreas. It is also found in neurons and may appear to act within the central nervous sytem (CNS) as a neuromodulator.

►Visceral Afferents

Cholesterol

Definition

A lipid molecule with a four-ringed steroid structure found in the cell membrane that affects membrane rigidity and water permeability.

►Membrane Components

Choline Acetyltransferase

Definition

Enzyme required to synthesize acetylcholine.

►Evolution of Subpallial Cholinergic Cell Groups

Cholinergic

Definition

Cholinergic refers to acetylcholine and neurons that secrete acetylcholine as a neurotransmitter.

►Acetylcholine

Cholinergic Brainstem

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Synonyms

Cholinergic neurons in the brainstem; Sources of acetylcholine in the brainstem

Definition

Cholinergic brainstem refers to neurons (neuronal cells) in the brainstem that synthesize and release acetylcholine as their neurotransmitter.

Characteristics

Identification of Cholinergic Neurotransmitter and Neurons in the Brainstem

In 1936, the English physiologist Sir Henry Dale and the German-Austrian-American pharmacologist Otto Loewy shared the Nobel Prize in physiology and medicine for their discoveries of ►acetylcholine (►ACh) as a neurotransmitter. In fact, ACh was the first chemical transmitter to be recognized as a neurotransmitter. In cholinergic neurons, the enzymes choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) are synthesized at the cell body and then move to the nerve terminals [1]. Terminals of the cholinergic neurons contain acetyl coenzyme A (acetyl-CoA), produced by an intermediary metabolic step, and choline, taken up from the synaptic cleft and other parts of the extracellular space by an active, sodium dependent, high-affinity transport system. In the nerve terminals, acetyl-CoA and choline are combined by the enzymatic activity of ChAT to synthesize ACh molecules [1]. These Ach molecules are stored within synaptic vesicles and are released in response to action potentials. Released ACh activates postsynaptic as well as presynaptic receptors. Since cholinergic neurons synthesize both ACh synthesizing enzyme, ChAT, and a degradation enzyme, AChE, the 1960s studies first aimed at the identification of brainstem cholinergic neurons attempted to do so by localizing cells containing the enzyme AChE. Later it was discovered that AChE is also synthesized by non-cholinergic neurons containing cholinergic receptors. It turns out that the presence of the ACh synthesizing enzyme ChAT is a more specific marker for the identification of cholinergic neurons. In the 1980s, for the first time, the cholinergic neurons in the brainstem were identified definitively with immunohistochemical staining of ChAT [2].

Anatomical Characteristics of Brainstem Cholinergic Cells

There are two categories of cholinergic neurons in the ►brainstem. Neurons in the first category have their cell bodies in the brainstem whereas their axons terminate in the periphery. This category of cholinergic cells is located in the hypoglossal nucleus, the nucleus ambiguus, the dorsal motor nucleus of the vagus nerve, the facial nucleus, the salivatory and lacrimatory complexes, the motor nucleus of the trigeminal nerve, the trochlear nucleus, the oculomotor complex, and the Edinger-Westphal nucleus. Another category of brainstem cholinergic neurons is completely contained within the central nervous system. This category of brainstem cholinergic cells is mainly located in the pontomesencephalic junction in two aggregates [2]. One aggregate of these cholinergic neurons is located in the pedunculopontine tegmentum (PPT, also called Ch5 sector) and another aggregate of neurons is located in the laterodorsal tegmentum (LDT, also called Ch6 sector). Cholinergic neurons within the PPT and LDT are medium to large in size (diameter ranging from 15 to 25 μm) [3]. These cholinergic neurons are variously shaped but are mainly fusiform, polygonal, and oval. Cholinergic neurons in the PPT are slightly more irregularly shaped than those in the LDT. The cytoplasm of these cholinergic neurons is highly developed and remarkably rich in organelles, including free ribosomes, rough and smooth endoplasmic reticulum, Golgi apparatus, and mitochondria [3]. The nucleus of these neurons typically contains large, dense, eccentric nucleoli with invaginated nuclear membranes.

Physiological Characteristics of Brainstem Cholinergic Cells

Physiological characteristics of brainstem cholinergic cells have been studied by recording extracellular-single-cell-unit (single-unit) activity of PPT and LDT neurons [4]. Single-unit activity recording is a technique that records extracellularly the occurrence and duration of action potentials of a neuron. The frequency of extracellularly recorded action potentials (number of action potentials per second) is expressed as firing rate (also called discharge rate). Increased firing rate of a neuron means increased physiological activity of that neuron and similarly decreased firing rate of a

neuron means decreased physiological activity. Based on the patterns of sleep-wake-state-dependent single-unit activity rates, five different types of cholinergic neurons have been identified in the PPT and LDT of cats and rats [4,5]. The firing rate of the first type of neurons, called ►REM-on cells, increases as the animal transitions from wakefulness to non-REM (NREM) sleep (►Non-REM Sleep) and then to ►Rapid eye movement (REM) sleep. The firing rate of the second group of neurons, called ►Wake-REM-on cells, increases during both wakefulness and REM sleep. The third group of neurons, ►Wake-on cells, begins to discharge seconds before sleep is terminated and then maintains a high discharge rate until the end of the waking period. This type of cell remains silent throughout the sleep period. The fourth group of neurons, called ►REM-off cells (also called PS-off cells), stops firing during REM sleep. The firing rates of the neurons in the fifth group, called state-independent cells, do not change as a function of sleep-wake behavioral states. The majority of the PPT and LDT cells are of REM-on and Wake-REM-on types. The durations of action potentials of these cholinergic cells are between 0.8 and 2.0 ms [5]. Another important physiological characteristic of a neuron is the mode of firing. Normally, a neuron fires in two different modes: tonic and bursting. In the tonic mode the neuron discharges as a single spike and in bursting mode the neuron discharges as a cluster of three to five action potentials within a very short period of time. In behaving rats, PPT and LDT cholinergic cells fire only in a tonic mode. In the cat, PPT and LDT cholinergic cells fire mostly in a tonic mode, but occasionally during REM sleep, about 5% of those cells also fire in a bursting mode.

Brainstem Cholinergic Cells as Source of Acetylcholine in the Brain

There are three different ways to identify cerebral sites that receive ACh from the brainstem cholinergic cells: (i) anatomically, by localizing the sites that receive axonal terminals of brainstem cholinergic cells, (ii) neurochemically, by measuring brainstem cholinergic cell activation-induced ACh release in different parts of the brain, and (iii) by combining electrophysiological and pharmacological techniques to identify brainstem cholinergic cell activation-induced postsynaptic cholinergic effects [6]. Brain areas that receive axonal terminals of the brainstem cholinergic cells have been identified by visualizing the movements of different tracers from the PPT and LDT cholinergic cells to other parts of the brain and vise versa. A limited number of studies have also measured brainstem cholinergic cell activation-induced ACh release in some areas of the brainstem and forebrain [6]. There are some studies that have used a combination of electrophysiological recordings and pharmacological techniques to identify the postsynaptic targets of brainstem cholinergic cells and the postsynaptic effects of ACh released from those brainstem cholinergic cells [7]. Collectively, those anatomical pathway tracing, ACh release, and electrophysiological-pharmacological studies have provided evidences that the PPT and LDT cholinergic cells are the main supplier of ACh for the entire brainstem and also the thalamus [6]. Those studies also provided evidence that the PPT and LDT cholinergic cells are part of the Ach source for several nuclei in the hypothalamus, basal forebrain, and limbic areas. Although the targets for Ach released from the cholinergic cells of the PPT and LDT are mostly common, some parts of the brain receive ACh from only the PPT or the LDT. For example, in the medial prefrontal cortex, the brainstem source of ACh is the LDT and in the suprachiasmatic nucleus the source of brainstem ACh is the PPT. Interestingly, the PPT and LDT cholinergic cells are not the direct source of ACh for the cerebral cortex. In summary, the brainstem cholinergic cells act as a source of ACh for many different parts of the brain but the brain areas and proportion of total ACh are area specific.

Functions of Brainstem Cholinergic Cells

There is some conclusive evidence to suggest that the cholinergic cells in the PPT and LDT are directly involved in the regulation of REM sleep [6]. REM sleep is characterized by a constellation of events including the following: (i) activated cortical EEG; (ii) marked atonia of the postural muscles; (iii) rapid eye movements; (iv) a theta rhythm within the hippocampus; (v) spiky field potentials in the pons [►pontine wave (P-wave)], lateral geniculate nucleus, and occipital cortex (also called ►ponto-geniculo-occipital (PGO) spikes); (vi) myoclonic twitches, most apparent in the facial and distal limb musculature; and (vii) pronounced cardio-respiratory and core body temperature fluctuations. Distinct cell groups located in the brainstem generate individual events of REM sleep. They are discrete components of a widely distributed network rather than a single REM sleep "center" [6]. For example, muscle atonia is executed by the activation of neurons in the ►locus coeruleus alpha, rapid eye movements result from the activation of neurons in the peri-abducens reticular formation, PGO waves emerge by the activation of neurons in the caudo-lateral peribrachial area of predator mammals and in the dorsal part of the nucleus subcoeruleus of prey mammals, hippocampal theta rhythm is produced via the activation of neurons in the pontis oralis, muscle twitches appear with the activation of neurons in the nucleus gigantocellularis (especially the caudal part), and increased brain temperature and cardio-respiratory fluctuations occur via the activation of neurons in the parabrachial nucleus.

The desynchronized cortical EEG signature of REM sleep, however, is executed jointly by the activation of neurons in the mesencephalic reticular formation and rostrally projecting bulbar reticular formation [6]. Each of these particular cell groups is simply a set of executive neurons for an individual sign. For the final expression of an individual sign, the relevant executive neurons employ a specific neuronal circuit unique to that REM sleep sign. In essence, each of these REM sleep signs has a separate, specialized network. Thus, each of these REM sleep signs could be modulated with multiple neurotransmitters at multiple sites within their circuits. Turn-on or turn-off conditions of REM sleep generating executive neurons are regulated by the ratios of available aminergic and cholinergic neurotransmitters within those cell groups [6]. The source of aminergic neurotransmitters is the locus coeruleus (LC) and raphe nuclei (RN), while cholinergic neurotransmitters, as stated above, originate from the LDT and PPT [6]. The activity of both aminergic and cholinergic cells is approximately equal during wakefulness and the onset of NREM sleep results in an equal reduction in activity. Therefore, during wakefulness and NREM sleep the ratio of aminergic to cholinergic neurotransmitters in REM sleep generators is proportionate. During REM sleep, however, aminergic cell activities are markedly reduced or absent and cholinergic cell activities are comparatively high. Thus, when a hypothetical ratio of aminergic and cholinergic neurotransmitters is low (1:1 ratio), the REM sleep sign-generators remain in the turned-off condition; however, when this ratio is high (0:0.65 ratio), the generators are turned-on to express REM sleep signs [5]. This is how the activity of PPT and LDT cholinergic cells regulate REM sleep. To initiate and maintain the activation of REM sleep sign generators, brainstem cholinergic cells in the PPT are activated by the stimulation of kainate-type glutamate receptors [6]. Activation of GABA-B receptors inhibits PPT cholinergic cell activity to terminate REM sleep [6].

Single-cell recordings, chemical stimulation, and anatomical pathway tracing studies also suggest that the activation of PPT cholinergic cells could promote wakefulness [6]. Single-cell recording studies examining sleep-wake state-dependent firing patterns in the PPT and LDT of behaving cats and rats identified the five aforementioned major groups of cholinergic cells: (i) REM-on, (ii) Wake-REM-on, (iii) Wake-on, (iv) REM-off, and (v) sleep-wake state-unrelated. Of those five categories of cells, Wake-REM-on cells are active during both wakefulness and REM sleep [5,6]. In contrast, the Wake-on cells were found to be active only during wakefulness. The presence of Wake-REM-on and Wake-on types of cells suggests that the PPT and LDT are involved in promoting wakefulness. A recent single cell recording study in freely moving rats has shown that the Wake-REM-on cell population within the cholinergic cell compartment of the PPT increases neuronal activity as a prelude to wakefulness and remains very active until 5–8 s before the end of wakefulness [5]. Consistent with this analysis, Ach release in the thalamus is highest during waking, slightly less during REM sleep, and at a minimum during SWS. The causal evidence that the PPT is involved in generating wakefulness came from local chemical stimulation studies [6]. Chemical stimulation studies have demonstrated that the activation of NMDA-type ►glutamate receptors within the PPT cholinergic cell compartment induces wakefulness. PPT and LDT cholinergic cells project directly to multiple wake-promoting areas of the forebrain via thalamo-cortical, hypothalamo-cortical, basalo-cortical pathways [6]. Activation of the PPT NMDA receptors promotes wakefulness by activating multiple wake-promoting areas of the forebrain. On the contrary, inhibition of PPT cholinergic cells reduces the total amount of wakefulness [6].

The projections from the PPT and LDT to the thalamic nuclei constitute a major component of the ascending reticular activating system [4,7]. Increased activity of these cholinergic cells increases the levels of ACh release in the thalamus. ACh is an excitatory neurotransmitter for the thalamo-cortical cells. Since those PPT and LDT cells are active during both wakefulness and REM sleep, ACh release from these brainstem cholinergic cells may play an important role in cortical activation during both waking and REM sleep. Indeed, the NMDA receptor-mediated activation of PPT cholinergic cells increases cortical activation [4,6]. Cortical activation is a prerequisite for cognitive functions, and thus, the activation of PPT cholinergic cells may contribute positively to cognitive processing. In summary, the normal functioning of the brainstem cholinergic cells in the PPT and LDT is involved in the regulation of REM sleep, wakefulness, and cortical activation processes.

Brainstem Cholinergic Cells and Disease

Although there is no known direct causal relationship between the patho-physiology of brainstem cholinergic cells and any disease condition, a number of degenerative neurological diseases involve brainstem cholinergic cells [8,9]. For example, both amyotrophic lateral sclerosis and Mobius syndrome involve degeneration of brainstem motoneurons. Parkinson's disease (PD) and progressive supranuclear palsy (PSP), which are both characterized pathologically by the loss of PPT neurons, share varying degrees of insomnia and motor dysfunction as clinical manifestations. More recently, using a transgenic animal model, it has been shown that cholinergic cell loss in the PPT may be a causal factor for a number of symptoms in Alzheimer's disease,

especially the disturbances in REM sleep [6]. It is also suspected that developmental abnormalities of PPT cholinergic cells during prenatal and early postnatal periods could be a significant contributing factor for the development of endogenous depression and schizophrenia in adolescence and adulthood [10].

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Cholinergic Fiber

Definition

A cholinergic fiber is the axon of an autonomic neuron that synthesizes acetylcholine. These include axons of some postganglionic sympathetic neurons, most postganglionic parasympathetic neurons, some enteric neurons and probably all preganglionic autonomic neurons. Many cholinergic fibers contain co-transmitters such as neuropeptides or nitric oxide, and acetylcholine may not necessarily be the primary neurotransmitter.

►Acetylcholine

Cholinergic Neurons in the Brainstem

►Cholinergic Brainstem

Chondrichthyans

Definition

Outgroup of remaining gnathostomes: include all cartilaginous fishes, i.e., elasmobranchs (sharks, skates and rays) and holocephalans (chimaeras).

►Evolution of the Brain: In Fishes
►Evolution of the Telencephalon: In Anamniotes

Chondrocytes

Definition

The metabolically active cells of articular cartilage that maintain the intercellular matrix.

►Articular Cartilage

Chondroitin and Keratan Sulfate Proteoglycans

Definition

Proteoglycans are a set of ubiquitous proteins found on cell surfaces, within intracellular vesicles, and incorporated into extracellular matrix. Both chondroitin and keratan sulfate proteoglycans are included in the proteoglycans family.

►Regeneration

Chondroitin Sulfate Proteoglycans (CSPGs)

Definition

CSPG are part of a larger family of proteoglycans that consist of a protein core and long sulfated

sugar residues (glycosaminoglycans, GAGs). Other family members are heparan sulfate proteoglycans, keratan sulfate proteoglycans and dermatan sulfate proteoglycans. The difference between the family members is due to the different sulfated GAG chains. CSPGs are expressed on the surface of most cells and in the extracellular matrix of most tissues. In the CNS, CSPGs such as brevican, veriscan, aggrecan, phosphocan, neurocan, NG2 and neuroglycan are expressed mainly by astrocytes and oligodendrocyte precursors. They play a role in cell migration, brain development, neurite outgrowth and axon path finding. After CNS injury, astrocytes that form the glial scar express increased amounts of CSPGs at the site of injury. CSPGs inhibit axonal regeneration, mostly due to the presence of the GAG chain, and contribute to the inhibitory effects of glial scar. Removal of the GAG chains by the enzyme chrondroitinase ABC reduces its inhibitory effect and promotes axon regeneration in the injured CNS.

►Inhibitory Molecules in Regeneration

Chondroitinase

Definition

Several bacteria have evolved enzymes which have the ability to digest chondroitin sulfate proteoglycans (putative components of the extracellular matrix that inhibits axonal regeneration). These are collectively called chondroitinase, followed by the capital letters A, B, C, indicating the sulfation forms of the chondroitin sulfate that they are able to digest.

►Regeneration
►Regeneration of Optic Nerve

Chondron

Definition

A chondron consists of a chondrocyte and its protective pericellular matrix and capsule.

►Articular Cartilage

Chorda Tympani (CT)

Definition

The chorda tympani (CT) is a branch of the intermediofacial nerve complex. It carries efferent parasympathetic axons to the submandibular ganglion to supply two major salivary glands (sublingual and submandibular glands). The CT also contains afferent gustatory axons supplying the fungiform taste buds of the anterior part of the tongue. Their nuclei are situated in the ganglion geniculi, but the first relay lies in the rostral part of the nucleus of the solitary tract.

►Neural Coding of Taste

Chordates

Definition

The taxon that is characterized by the presence of a notochord. The extant members of this taxon comprise the cephalochordates (amphioxus), urochordates (sea squirts), and vertebrates.

►Evolution of Brain: at Invertebrate–vertebrate Transition

Chordotonal Organ

Definition

A type of proprioceptive stretch receptor in crustaceans and insects consisting of thin, elastic strands of connective tissue stretched between adjacent body regions and comprised of individual mechanosensory units called scolopidia.

►Invertebrate Ears and Hearing

Chorea

Definition

Literally meaning “dance” in Greek, chorea resembles exaggerated fidgetiness with fast writhing movements.

The movements are usually generalized and purposeless, although in mild cases, chorea may be blended into natural movements and appear purposeful. Choreoathetosis is the term used when the movements have a slower writhing component. Chorea is seen in Huntington's disease, can be caused by chronic use of levodopa in Parkinson disease, and occurs in the rare condition known as Sydenham chorea (also knows as St. Vitus' dance).

►Huntington's Disease
►Parkinson Disease
►Sydenham Chorea

Chorea Chronica Progressiva

Definition

►Huntington's Disease

Chorea Hereditaria

Definition

►Huntington's Disease

Chorea Minor (Chorea Infectiosa, Chorea Rheumatica)

Definition

►Sydenham Chorea

Chromaffin Cells

Definition

Cells in the adrenal medullary tissue that are derived from the neural crest ectoderm.

Chromatic Processing

►Color Processing

Chromatic Vision

►Color Processing

Chromatin Immunoprecipitation and the Study of Gene Regulation in the Nervous System

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Synonyms

Chromatin immunoaffinity precipitation; ChIP; Chromatin immunopurification

Definition

Chromatin immunoprecipitation (ChIP) is a biochemical technique wherein antibodies, usually directed to ►transcription factors, are used to immunoprecipitate proteins (the specific transcription factor of interest or proteins bound to that transcription factor in a protein complex) bound to chromatin, usually genomic DNA (gDNA) sequences *in vitro* or *in situ*. The isolated gDNA fragments are likely to encode transcriptional regulatory units (promoters, enhancers, repressors) and can be used to identify direct transcription factor targets *in vivo*. Various methods are available to ►cross-link proteins to DNA. The ChIP procedure enables immuno-enrichment of putative target DNA sequences bound to the transcription factor *in vivo*. Subsequently, the identified sequences must be characterized to validate specific protein-DNA interactions *in vitro*, using electrophoretic mobility shift assays (EMSA), and their functional significance by implementation of gain and loss-of-function strategies both *in vitro* using reporter gene assays, and *in vivo* using transgenic animals or ►interfering RNA approaches.

Increasingly, the ChIP procedure has been quantified (►qChIP) or coupled to various sequencing (ChIPSeq) or array technologies, including cDNA or oligonucleotide microarrays used for expression profiling, ►promoter arrays, ►CpG island arrays, and ►tiling arrays, in order to identify the target sequences as well as ►consensus binding motifs in a high-throughput

manner. These technologies are often grouped together under the term ►ChIP-chip assays. ChIP methodologies have enabled investigators interested in nervous system development and function to study gene regulation under physiologic conditions, thereby permitting the identification of gene networks directly regulated by the transcription factor of interest. To date, transcription factors under study have included: ►homeobox proteins, ►helix-loop-helix (HLH) proteins, ►p53, ►E2F, and ►NF-κB.

►ChIP-chip technologies

- ChIP – cDNA or oligonucleotide microarrays
- ChIP – promoter microarrays
- ChIP – CpG island microarrays
- ChIP – tiling microarrays

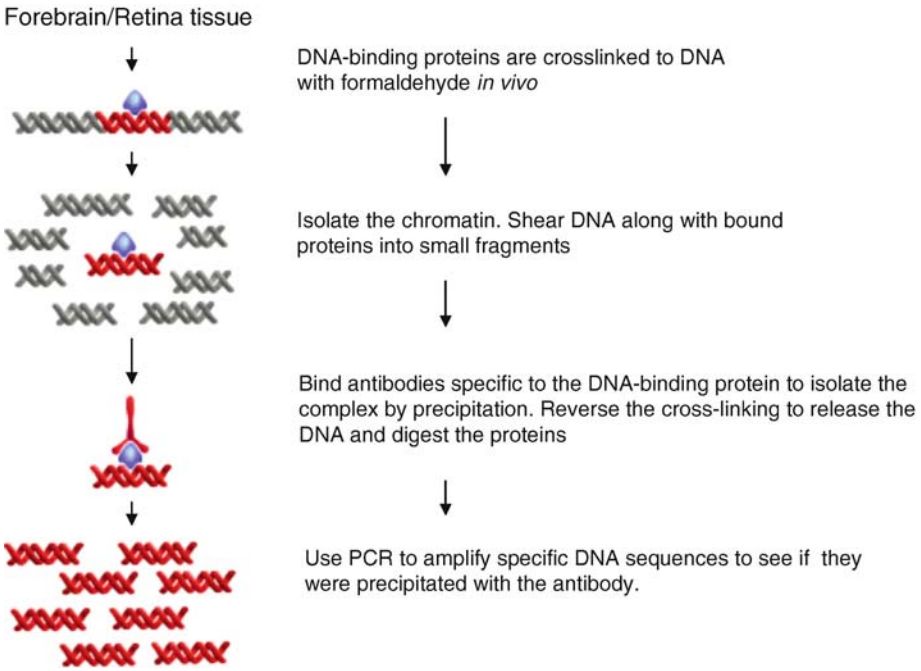
Characteristics

Description of the Process

A major advance towards the identification of target genes of specific transcription factors was the development of ChIP [1]. ChIP involves a biochemical rather than genetic approach to the identification of direct target genes. Unlike cDNA microarray analysis, ChIP isolates direct targets from relevant tissues under physiologic conditions [2]. Gould et al. [1] used an antibody to the *Ubx* homeobox gene product to immunopurify *Ubx* bound to DNA sequences from soluble chromatin. After immunoprecipitation (IP), the complexes were disrupted and the released genomic DNA (gDNA) fragments were cloned. The DNA fragments isolated by ChIP were enriched for sequences matching defined ►homeodomain binding sites and used to screen genomic DNA libraries for transcription units. Modifications of the ChIP protocol include stabilization of DNA-protein adducts in intact nuclei by cross-linking using ultraviolet (UV) light, formaldehyde (cross-links protein to DNA and protein to protein) and cisplatin, a chemotherapy agent that cross-links protein to DNA [3]. Utilizing these methods, homeodomain targets have been isolated and these targets include: homeobox genes, other transcription factors, growth factors, adhesion molecules, and secreted proteins. Until recently, the search for homeobox targets in vertebrates has not been as productive as in *Drosophila melanogaster*. Although several candidate genes have been identified using *in vitro* and tissue culture methods, the significance of these interactions *in vivo* remains to be confirmed. Takahashi's group also modified the ChIP approach to identify *mgl-1*, a ►tumor suppressor gene and putative adhesion molecule, as a downstream target of HOX-C8 from mouse spinal cord [4], showing that it is possible to isolate other direct vertebrate homeobox gene targets.

The most widely applied ChIP method is adapted [4,5] and modified by our group [6] (refer to Fig. 1).

►Optimizing the ChIP procedure



Chromatin Immunoprecipitation and the Study of Gene Regulation in the Nervous System.
Figure 1 Schematic outline of the chromatin immunoprecipitation (ChIP) procedure.

- Use sensitive and highly specific antibodies to the transcription factor
- Use antibodies with high binding affinities
- Use antibodies that work under varying conditions of tissue fixation and/or cross-linking
- Vary time of exposure to determine optimal duration of cross-linking protein to DNA
- Vary concentrations of the cross-linking reagent to favor protein-DNA complex formation
- Use cells obtained from embryonic tissues or the adult nervous system where peak temporal and spatial expression of the transcription factor occurs

We have optimized cross-linking by reducing paraformaldehyde concentration from 4% to 1% and decreasing the duration of cross-linking from overnight to 2 h to promote protein-DNA interactions [6]. Paraformaldehyde is used to cross-link protein to DNA. As input material, tissue that expresses the transcription factor of interest (such as embryonic day 13.5 (E13.5) ►ganglionic eminences that highly express members of the ►*Dlx* homeobox gene family) is isolated and freely dissected using a stereomicroscope. Ideally, 1–2 × 10^7 cells are required, but the amount of input material depends upon the relative abundance of the transcription factor. Tissues are incubated, cross-linked at 4°C with 1% paraformaldehyde, then homogenized, sonicated to yield solubilized nucleoprotein complexes, and centrifuged. Shorter incubation times with the cross-linking reagent may yield increased quantities of DNA bound to protein and it is recommended that the investigator perform time course experiments [6]. The supernatant is incubated with protein A±G sepharose bound to antibodies specific to the transcription factor under study. The bound complexes are eluted following reversal of cross-linking by heating at 65°C, dialyzed, then incubated with RNase and proteinase K. Proteinase K treatment removes the antigen-antibody complexes, leaving only genomic DNA fragments that are directly bound to transcription factor proteins *in vivo*. Following purification, gDNA fragments can be subcloned to generate a ChIP library, directly sequenced or used as input material for ChIP-chip assays. Controls may include immunoprecipitation of tissue that does not express the transcription factor at all (such as embryonic hindbrain for *Dlx* genes or embryonic heart for *Pax6*). Other investigators have used tissues derived from mutants for the specific transcription factor as a negative control. Control immunoprecipitations without primary antibody and with an unrelated polyclonal antibody are also recommended. The average size of the cloned gDNA fragments is approximately 300 base pairs [4].

Higher Level Processes

ChIP Libraries and ChIP-Sequencing

The ►ChIP library approach has been used as a means of high-throughput screening to identify the targets of homeobox genes. A ChIP library was constructed for the Drosophila homeoprotein Engrailed using a UV-cross-linking method in which 203 Engrailed binding sites within intergenic regions or introns were identified [7]. The observation of transcription factors frequently binding within introns is consistent with previous reports. Many identified potential target genes are involved in key developmental pathways, including axonal guidance [7]. Sets of replica library filters from gDNA target libraries developed following cross-linking can be hybridized with randomly selected clones. Clones that hybridize to multiple plaques may be screened by genomic Southern hybridization to determine the presence of repetitive DNA sequences (multiple bands or a smear of hybridization in the lane). Unique sequences give a single band and are likely to contain candidate regulatory sequences that can be further characterized [4].

Another means to rapidly analyze all gDNA fragments immunoprecipitated through the ChIP procedure is to identify DNA fragments bound to protein by direct DNA sequencing, using a method called ►ChIPSeq [8]. Johnson et al used a monoclonal antibody to neuron-restrictive silencing factor (►NRSF), also known as repressor element-1 silencing transcription factor (REST), to identify 6,718 single NRSF binding sites in the genome using criteria of at least 13 independent sequence reads and a fivefold enrichment relative to control DNA samples derived from chromatin not treated with the NRSF antibody. Since NRSF/REST silences neuronal gene expression in neural progenitors as well as non-neuronal cell types, this high-throughput sequencing approach shows promise as a means to identify the direct targets of other transcription factors important to mammalian nervous system development and function [8].

ChIP-Chip Assays

Unbiased mammalian ►promoter microarrays are not readily available due to insufficient annotation of regulatory sequence information. Nevertheless, attempts have been made to construct partial proximal promoter arrays of human cells. One group constructed a human proximal promoter array representing 13,000 genes [9]. The 13,000 proximal promoters were selected based on annotated transcription start sites. Despite these initial successes, the mammalian promoter array is still in its infancy due to the bias of how the promoter is defined and isolated in these arrays. Many regulatory elements, such as enhancers and silencers are located distal to transcription start sites, upstream or downstream of the coding region, or in intronic regions.

►CpG island arrays have also been generated to approximate promoters in the human genome [2,10]. CpG-rich sequences or CpG islands are associated with transcriptional activities. Weinmann et al. [2] have

successfully applied ChIP to isolate targets of the transcription factor E2F, including coupling of ChIP to CpG island microarray analysis. In this CpG array based ChIP-chip experiment, E2F binding targets were studied in HeLa cells [2]. Interestingly, within the 68 unique targets identified from the ChIP-on-chip screening, many targets were associated with DNA repair and recombination rather than cell cycle control, suggesting that the use of specific "chips" after ChIP may yield different yet overlapping classes of transcriptional target sequences. CpG island arrays are currently hampered by noise due to antibody specificity and the bias of the constructed array which only contains a representation of all CpG islands selected based upon the hypermethylation status of the sequence [2]. ►Tiling microarrays provide an opportunity to examine transcription factor binding sites in a truly unbiased fashion. However, dozens of arrays are required to adequately represent the mouse and human genome and the costs of such experiments may be prohibitive.

Following ChIP, Linker-Mediated PCR is used to amplify the isolated DNA fragments. The PCR products are then labelled with either Cy3 or Cy5, using indirect labelling with aminoallyl dUTP and random priming of the template. These labelled PCR products can be hybridized to mouse or human CpG island spotted arrays. Slides are then scanned using a microarray scanner and associated software. Spots for which the ratio of the Ab(+):Ab(−) control is greater than 1.5 (having a signal more than twice background) may be considered significant. CpG island and tiling arrays, scanners and software are available in the public and private sectors. Additional control experiments, such as performing ChIP (with and without antibody) on a negative tissue control prior to hybridization on the CpG island arrays, should also be performed. Of interest, ChIP-gDNA library and the ChIP-CpG island array technologies applied to embryonic mouse tissues may yield different yet overlapping lists of target genes (Cheng, Pind and Eisenstat, unpublished observations), similar to findings reported using human cells.

Regulation of the Process

Cisplatin or *cis-diamminedichloroplatinum (II)* will not cross-link protein to protein and may be a more selective cross-linking reagent than formaldehyde compounds [6]. The cell lysate is added to hydroxylapatite resin. RNA and proteins not cross-linked to DNA are washed away. The cross-linking is reversed by incubating in thiourea, releasing proteins from the hydroxylapatite, while the DNA will remain bound. ChIP using cisplatin cross-linking of protein to DNA may isolate different gene targets than by paraformaldehyde cross-linking, such as those associated with the ►nuclear matrix. It is reported that transcriptionally active genes are nuclear matrix associated.

Function

The utilization of biochemical approaches such as ChIP provides several ►advantages. Identified target genes are directly downstream and are derived from physiological transcription factor-DNA complexes obtained *in vivo*. The isolated gDNA fragments may be from transcriptional regulatory elements of previously identified or novel genes. ChIP may be applied to diverse species, including *Drosophila melanogaster* and vertebrates. The advantage of cross-linking is preservation of a naturally existing (*in situ*) protein-DNA interaction. Identification of a transcription factor consensus binding sequence using ChIP-chip arrays may be more efficient than by screening random oligonucleotide pools.

Chromatin immunoprecipitation does have several ►limitations. The choice of the cross-linking reagent may influence whether targets are indirectly or directly downstream. IP screens require specific antibodies and require the construction of separate DNA libraries for each protein for which targets are sought and these libraries may be hampered by low cloning efficiency. It might be difficult to identify targets that interact with the regulatory protein in only a few cells or during brief developmental periods. It may be necessary to perform ChIP at several developmental time points to obtain different functional classes of transcription factor targets. Another problem may be that there is promiscuous binding. One way to reduce the non-specific DNA obtained from the ChIP procedure is to subtract the ChIP-DNA with input DNA before sub-cloning. In addition, binding may be significantly distant from the coding region As well, since most homeodomain proteins, for example, bind to a consensus TAAT core motif, many of the immunopurified fragments may not be specifically regulated by the homeobox gene itself. Finally, multiple factors may be required for the regulated expression of the target gene.

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Chromatin Immunopurification

►Chromatin Immunoprecipitation and the Study of Gene Regulation in the Nervous System

Chromatolysis

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Synonyms

Axon reaction; Retrograde degeneration

Definition

The term chromatolysis (chroma: color; lysis: disintegration) refers to the disintegration or dispersal of the basophilic nissl bodies (►nissl body). The reaction takes place in the neuronal cytoplasma following ►axotomy or other traumatic or metabolic nerve injuries. Dispersal of the basophilic Nissl bodies due to disintegration of the stacked rough endoplasmatic reticulum is only one of many changes of the neuronal cell body following axotomy [1]. In this text we have chosen to embrace all the morphological changes taking place following axotomy [2].

Characteristics

Quantitative Description

The morphological reaction of chromatolysis has been extensively studied for more than a century in experimental animal models. It was Nissl in 1894 and Marinesco in 1898 who first described the reaction using light microscopy. The classical chromatolytic appearance of the neuronal cell body can easily be recognized using light microscopy and cresyl violet or toluidin stained tissues. It includes disintegration of the basophilic Nissl bodies to a dust like appearance, peripheral condensation of basophilic substances, eccentricity of the nucleus, a basophilic nuclear cap and crenation (folding) of the nucleolemma. Often the cell body is surrounded by activated small basophilic sattelite glial cells (sattelitosis). Swelling of the cell body is frequently reported as part of the chromatolytic reaction in early neurocytological studies. In a series of studies from our own laboratory using modern stereological methods we have shown an initial cellular shrinkage amounting to approximately 30% following nerve crush and nerve transection [3,4]. In surviving cell bodies shrinkage was followed by a return to normal cellular dimensions after 3–5 months [4]. The initial morphological changes appear during the first 2–5 days following nerve damage [2] and progress during the following weeks followed by a gradual recovery with return to normal cell morphology among surviving cells. Four days after axotomy no significant cell loss can be detected. After 15 days the cell loss amounts to 31% without further progression during the following weeks.

Morphology

Chromatolysis is observed in neuronal cells in the peripheral and central nervous system. Furthermore, the reaction is not confined to the neurons but also involves the surrounding glial cells. Some authors refer to this as an activation of the sattelitic glial cells and in the light microscope it is recognizable as sattelitosis, the neuron being surrounded by basophilic glial cells. The role of the activated glial cells is controversal, but it is hypothesized that they play a key role in supplying the neuron with neurotrophic growth factors which it is denied because of damage to the peripheral axon.

Sattelitosis should not be mistaken as an inflammatoric response. There is no immune reaction surrounding the neurons and when cell death occurs it is by apoptosis and not by necrosis.

Ultrastructure

Chromatolysis leads to intracellular reorganisation of the cytoplasma and its organelles. Electron microscopic studies have only provided sparse information as to the actual changes of the organelles, and the details are beyond the scope of this essay. The nissl bodies, smooth endoplasmatic reticulum, lysosomes, cytoskeleton, nucleus and nucleolus are all influenced by the shift to a state of regeneration with increased synthesis of ►household proteins. The characteristically morphological changes occurring in the cell (eccentricity of the nucleus and peripheral displacement of basophilic substances) has traditionally been hypothesised to be caused by osmotic swelling. Later studies, however, revealed an abundance of nissl body-free cytoskeletal components stockpiled in the cytoplasma of axotomised neuronal cells [5] believed to cause the displacement of the organelles, including that of the nucleus.

Structural Regulation

Chromatolysis is a temporary condition of regeneration in response to a harmful stimulus rather than a step in a chain of inevitable events leading to cell death. Axotomy, traumatic, pathological as well as toxicologic conditions can result in a condition leading to chromatolysis. With regard to axotomy, which by definition leads to loss of the axon terminal, the chromatolytic regenerative state is supposed to be caused by massive intracellular reorganization caused by the need to initiate a growth program for the formation of the axonal growth cone to replace the amputated axonal terminal [5,6]. Dependent on the harmful stimulus a fraction of the cells will die, by apoptosis, and another fraction will regenerate and resume normal morphology and function when possible. Neurons in the central nervous system seem very vulnerable to traumatic damage whereas neurons in the peripheral nervous system seem rather resilient to traumatic damage and in most cases regenerate dependent of the severity of the trauma. In a series of experiments performed in our laboratory, permanent central nerve damage of spinal nerves in rats lead to a reduction of L5 dorsal root ganglion (DRG) neuronal cells of 26% after 3 months whereas 46% of the cells were chromatolytic. In diabetic rats there was no increase in cell loss and 46% of the remaining neurons were also chromatolytic [7]. This indicates that in spite of a severe trauma of the spinal nerve, 1 cm distal to the DRG only one fourth of the neurons succumb to apoptosis, and roughly half of the remaining cells are in a state of chromatolysis with the potential to survive.

The amount of loss of neuronal DRG cells is dependent on the distance to the DRG. In sciatic nerve axotomy in rats the DRG cell loss is smaller than after spinal nerve axotomy and occurs later [8].

Neurotropic Factors

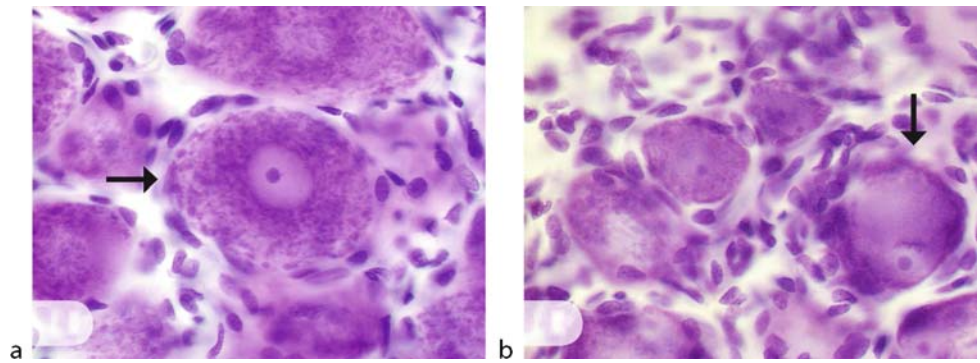
Structural damage as well as other pathological conditions can cause a neuron to enter a state of chromatolysis. The signal for this transformation has not yet been identified but strong evidence points toward loss or reduction of neurotrophic factors derived from the periphery [1]. ►NGF has been suggested to play a role because experiments have shown that axotomy-induced chromatolysis of sympathic ganglia cell bodies in vitro is blocked by application of NGF and that application of NGF antisera leads to axotomy like changes [1]. Other neurotrophic factors might play a role and up and down regulation of neurotrophic receptors in pathological conditions might well be involved.

Process Regulation

The signal leading to chromatolysis has been debated for decades, and in comprehensive reviews during the 70's [2,9] not less than ten possible candidates were presented. Strong evidence, however, suggests an important role of axonally retrogradely transported signaling proteins. In reviews, [1,6] the lack of retrogradely transported peripheral trophic factors important for the continuous upheaval of the cell body integrity as well as the presence of peripheral electrical stimuli via calcium influx en masse and retrogradely transported chromatolysis inducing proteins are discussed. It seems likely, however, that the signal for chromatolysis is in part the lack of retrogradely transported peripheral trophic factors usually achieved from the axon terminal as well as traumatic initiated electrical or biochemical stimuli of the cell body. In contrast to the traditionally held belief that all neuronal proteins are produced centrally and anterogradely transported to the axon and the axon terminal, new research indicates that protein synthesis capacity is present in the axon [6,9], and that damage to the axon might trigger translation of mRNAs. Peripherally produced peptides possibly play an important role in initiating the chromatolytic reaction in response to axonal damage by retrogradely transporting to the cell body, including the formation of a growth cone for regeneration of the axon terminal [6,10], the latter only being an ability characteristic of the peripheral nervous (Fig. 1).

Function

Chromatolysis is considered to be a state of regeneration in damaged neuronal cells characterized by increased synthesis of cytoskeletal and other housekeeping proteins with down regulation of neurotransmitter-related enzymes and receptors. The state is a shift from external functioning to internal build up and the surface of the cell is covered by glial profiles from activated sattelite glial cells leading to a temporary loss of most presynaptic dendritic terminals.



Chromatolysis. Figure 1 Non-chromatolytic dorsal root ganglion cells with preserved nissl substance and a centrally placed nucleus (a). Chromatolytic dorsal root ganglion cells showing disintegration of nissl substance, displacement of nucleus and sattelitosis of glial cells around the neuronal cell body (b).

Pathology

The bulk of experimental work regarding chromatolysis has been performed in animal models inflicting physical (axotomy or chrush [3,4]), thermal or chemical (acyrylamide intoxication) damage to the peripheral (DRG or sympathetic ganglions) or central nervous system (visual cortex and retinal ganglia or olfactory bulb). Chromatolysis is, however, observed is part of many disease processes including multiple schlerosis, porphyria, pellagra, amyotrophic lateral sclerosis and poliomyelitis.

Therapy

Chromatolysis is a regenerative cytologic response to harmful physical or metabolic exposure. In accordance with this statement there is no information about conditions in which chromatolysis is the primary pathology. In traumatic injury it seems attractive to support regrowth of damaged axonal or dendritic processes by supplying patients with neurotrophic growth factors, or by manipulation of axonal protein synthesis, growth cone formation and propagation. The knowledge of this field is still limited and on a strictly experimental basis. In the future, however, stimulation and manipulation of chromatolysis and regeneration of neuronal cells might prove to be a new approach in posttraumatic neurology.

►Neuronal Changes in Axonal Degeneration and Regeneration

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Chromophore

Definition

In biological molecules that serve to capture or detect light energy, the chromophore is the moiety that causes a conformational change of the visual pigment. Linked with an opsin protein, the chromophore is based on either the vitamin A1 aldehyde, 11-cis-retinal (rhopsin) or the vitamin A2 aldehyde, 11-cis-3, 4-dehydroretinal (porphyropsin).

►Photopigments

Chromosome

Definition

A chromosome is a single large linear DNA macromolecule in a cell's nucleus, which contains genes, regulatory elements and other nucleotide sequences.

Chronaxy

Definition

Duration that a rectangular direct current (DC) current of double rheobase strength must flow in order to elicit an action potential.

►Action Potential
►Rheobase

Chronic Daily Headache (CDH)

Definition

Headaches which occur more than 4 h/day, more than 15 days/month. Most CDH is medication overuse headache, though chronic tension-type headache, new daily persistent headache or hemicrania continua may occur.

►Headache

Chronic Endotoxin Exposure

Definition

Prolonged exposure to lipopolysaccharide, the major component of the outer membrane of gram negative bacteria, to mimic a chronic infection; exposure via chronic systemic infusion or repeated bolus doses.

►Prenatal Brain Injury by Chronic Endotoxin Exposure

Chronic Insufficient Sleep Syndrome

Definition

Insufficient nocturnal sleep, which can be behaviorally or environmentally induced, and results in sleep deprivation and reduced waking alertness.

►Alertness Level

Chronic Nerve Denervation

Definition

The condition of the nerve distal to injury which is still devoid of axons. Schwann cells in the chronically denervated nerve undergo progressive deconditioning, atrophy and even loss. They thus become increasingly incapable of supporting axonal regeneration.

►Peripheral Nerve Regeneration and Nerve Repair
►Schwann Cell
►Schwann Cells in Nerve Regeneration

Chronic Pain

Definition

►Pain

►Development of Nociception

Chronic Peripheral Neuropathies

Definition

Chronic peripheral neuropathies manifest themselves in various forms, and their severity may range from mild to fatal. There are many etiologies, including genetic causes such as ►Charcot-Marie-Tooth disease and acute intermittent porphyria, metabolic diseases such as vitamin B12 deficiency and diabetes, nutritional disorders such as ►thiamine deficiency and alcoholism, immunological diseases such as amyloidosis and

plasma cell diseases, intoxication e.g. by lead, and carcinomas e.g. of the lung.

►Charcot-Marie-Tooth Disease
►Diabetes mellitus
►Thiamine (Vitamin B1) Deficiency
►Vitamin B12 Deficiency

Chronobiology

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Definition

Chronobiology is the study of biological processes with respect to time, specifically concerning the four environmental rhythms, namely tide, day, moon and season. It is not concerned with linear time-dependent processes such as aging.

Characteristics

Chronobiology refers to temporal aspects of life which have been shaped by regular, predictable and repeating structures in the environment. On earth, four geophysical time structures cycle in a predictable way: the annual cycle with its seasonally changing ►photoperiods (day length) and temperature; the lunar cycle with its changing nocturnal light levels and weak gravitational forces (that are probably irrelevant for non-tidal organisms); the daily cycle with its changing light and temperature levels; and the tidal cycle with concurrent gravitational forces leading to alternating exposure of coastal terrain to water and air. These four temporal structures have shaped biological rhythms (or biological clocks) through evolution. When shielded from their corresponding environmental cycles, all four biological rhythms are capable of oscillating with their own period which is always close to that of the environmental cycle (365.25 days, 28.5 days, 24 h and 12.5 h, respectively). Because of their moderately deviating endogenous periods, they are called circa-rhythms (circ-annual, circa-lunar, circa-dian, and circa-tidal). The environmental signals that synchronize biological clocks to the exact period of their respective environmental counterpart are called ►zeitgebers. The complex, active biological mechanism enabling this synchronization is called ►entrainment.

The biological mechanisms underlying the endogenous circannual, circa-lunar, circadian or circa-tidal clocks are the subject of intensive experimental (chronobiological) research. Most chronobiological research concerns daily and annual rhythms.

Daily Rhythms

By far the most studied biological rhythm is the ►circadian rhythm (Latin: *circa* – about – and *dies* – a day). It is an excellent example of how circa-rhythms affect living systems at all levels of biology – from gene expression, hormone secretion and physiology to complex behavior. The circadian clock represents internal time-of-day and ensures that the appropriate biological functions in cells, tissues and organs occur at the right time in relationship to other endogenous processes and to the external environment.

The signature of circadian rhythms is their persistence in constant conditions, (shielded from all zeitgebers) revealing their ►free-running period. Examples of circadian rhythms are the sleep-wake behavior in humans and other animals, leaf movement in plants, fungal spore formation, and virtually all of gene expression in cyanobacteria, to name only a few. Circadian rhythms are ubiquitous, i.e., they have been identified in organisms of all phyla, and, in each organism, they modulate all aspects of biology [1].

In spite of being built by different cellular and molecular components in different organisms (see below), circadian rhythms share basic properties. They are (i) rhythmic and (ii) self-sustained (i.e., non-dampened), (iii) with a circa 24-h period in constant conditions; (iv) circadian rhythms are both robust in their amplitude (sufficient to drive output rhythms) and precise in their period (though not exact, circadian rhythms have been shown to continue for years with deviations of only minutes [2]); (v) their period is compensated against spurious environmental changes (e.g., of temperature or nutrients); (vi) circadian rhythms can be synchronized by appropriate environmental signals (zeitgebers). This synchronization is a complex, active process called entrainment. Under natural conditions, circadian clocks are perfectly entrained to the 24-h rotation of the Earth by using the environmental changes that have shaped circadian clocks through evolution (predominantly light, but poikilotherms also use temperature) as zeitgeber signals.

Annual or Seasonal Rhythms

Similar to the day, the year also shows distinct characteristics in its temporal structure. With growing distance from the equator towards the poles, seasonal changes in day length become increasingly obvious (even at the equator, seasonal progression is apparent, for example, by different amounts of rain). Two different chronobiological strategies allow organisms to adapt their physiology and behavior to the progression of seasons: the circannual clock and photoperiodism.

Similar to the circadian clock, a circannual clock represents internal time-of-year and ensures that the appropriate biological functions in cells, tissues and organs occur at the right time in relationship to both other

endogenous functions and to external time-of-year. Similar to the case of the circadian clock, alterations in light and dark are the predominant zeitgeber that entrain ►circannual rhythms – in this case, alterations in changing photoperiod. Circannual clocks can run free when photoperiod is kept constant, slightly deviating from 365.25 days (some circannual clocks only show a free-run in a specific constant photoperiod of, for example, 10 h light and 14 h darkness, LD10:14 [3]).

While the entrained circannual program ensures continuous adjustment of immunological, metabolic and behavioral processes to seasonal environmental changes, photoperiodism opens a once-a-year window, which is called the critical photoperiod, triggering a (photoperiodic) response. In most plants and animals, this response is related to reproduction. The mechanisms that detect this critical photoperiod involve the circadian system as an internal reference (abnormal photoperiodic timing is typical for ►circadian clock mutants [4]). The sensitivity to certain critical photoperiods requires a previous sensitization by, for example, short days. Hamsters provide an impressive example for a photoperiodic response, as they rapidly enlarge testes and become reproductive following exposure to days with photoperiods over 12 h [5].

Compared to the circadian program, we know far less about the anatomical structures, genes and molecular mechanisms which form the basis of both circannual rhythmicity and photoperiodism.

Molecular Chronobiological Mechanisms

Genetics has been broadly applied to describe the circadian clock mechanism, an approach pioneered in the lab of Seymour Benzer. Mutant screens have revealed a complex network of so-called ►clock genes – genes that, when mutated or deleted, change at least one of the six fundamental properties of circadian rhythms (see above). Clock genes, involved in generating the circadian rhythmicity at the cellular level, form a transcriptional-translational negative feedback loop. Activators control the production of gene transcripts leading to proteins which undergo a progressive modification (mainly phosphorylation) and eventually feed back to inhibit their own transcription. In the cyanobacterial system, circadian oscillations have been definitively shown to depend on rhythmic phosphorylation and dephosphorylation of a set of proteins, a process which even persists in a test tube [6]. It is not clear how this may relate to eukaryotic molecular clocks.

Clock genes have been identified in model genetic organisms from all phyla. Interestingly, animals, plants, fungi and bacteria all feature distinct gene sets, which nonetheless function similarly on the molecular level. This suggests that these are species-specific adaptations to their environment, rather than evidence of a primordial, common clock.

Human Chronobiology

One of the easiest ways to understand chronobiology is to recall common human daily behaviors. For example, the human ►sleep-wake cycle occurs once per 24 h when entrained but runs free (with a circa 24-h period) when shielded from zeitgebers. There is, however, a tremendous difference in *when* sleep occurs in different individuals. The temporal differences in these so-called chronotypes are not restricted to sleep, but extend to other clock-controlled processes, such as melatonin or cortisol production. Within a population, the frequencies of different chronotypes show an almost normal distribution, reflecting that chronotype is a multi-genic, highly complex trait. Chronotypes result from individual differences in entrainment characteristics due to a variety of reasons: within the population there are polymorphisms or mutations in clock genes [7]; the late-to-bed, late-to-wake teenager is well known to all of us, and it reflects a systematic effect of development on the circadian clock [8]. From childhood to adolescence, the clock entrains progressively later, a trend that reverses – at the population level – at around the age of 20; there are gender differences in chronotype also, at least until the age of menopause, with females typically being earlier chronotypes than males; exposure to strong or weak zeitgebers also determines when the clock is entrained within the daily cycle. People who work outside in broad daylight are generally earlier chronotypes than office workers [8]. Thus, genes, environment, age and gender all contribute to chronotype.

The implications of chronotype are manifold. If chronotype, for example, is not incorporated into medical practice, results of tests or the efficacy of treatments may differ merely due to the patient's chronotype. Chronotype is also a quality of life issue. The more discrepancy between internal and external time (e.g., between an individual's circadian timing and his or her work hours), the more sleep debt accumulates during the work-week, culminating in a chronic "social jetlag." The larger this social jetlag, the more likely an individual is to be a smoker, indicating that a chronic jetlag acts as a stressor [8].

Chronobiology Concerns all of Biology

Because chronobiology has an impact on broad aspects of an organism's biology, it represents a scientific specialty similar in scope to development or reproduction. Circadian rhythms are a fundamental property of all organisms (with few exceptions). The concept of selective advantage due to increased fitness is inherent to evolutionary theory. The adaptive advantage of biological clocks lies in the benefit of being able to anticipate environmental changes. The activity of animals is frequently restricted to certain times of day, and straying outside of these domains can increase the risk of predation, for instance [9]. Sessile organisms

such as plants and fungi also benefit from prediction of temperature, nutrient, or humidity changes. The fitness concept was recently substantiated in vitro using cyanobacteria, showing that a circadian oscillation with a period similar to the environmental one is more successful [10]. Similar adaptive advantages hold for all circa clocks, whereby organisms prepare for seasons, tides or nocturnal light levels.

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Chronobiotics

Definition

A biological compound that can alter parameters (phase, period or amplitude) of circadian oscillators, or their responsivity to other inputs, thereby changing the phase relationship between circadian rhythms and local time, or the rate at which circadian rhythms are resynchronized following a shift of local time (e.g., transmeridian jet travel).

►Circadian Rhythm
►Human Circadian Timing System

Ciliar Body

Synonyms

Corpus ciliare; Ciliary body

Definition

Ciliary body of the eye. Contraction of the circular ciliary muscle results in relaxation of the lens ligament (zonal fibers), so that the lens can follow its inner elasticity and thicken. This increases its refractive power, needed for focusing on close objects. If conversely, the ciliarymuscle is relaxed, the eye is distant accommodated.

►Eye

Ciliary Ganglion

Synonyms

►Ganglion ciliare; ►Ciliary ganglion

Definition

Parasympathetic ganglion, some 2 cm behind the eyeball. The postganglionic fibers innervate, inter alia, two intraocular muscles:

- Ciliarymuscle (accommodation)
- Sphincter of pupil muscle (adaptation)

►Nerves

Ciliary Neurotrophic Factor (CNTF)

Definition

►Neurotrophic Factors

Ciliary Neurotrophic Factor Receptor (CNTFR)

Definition

Following ciliary neurotrophic factor (CNTF) binding, the CNTF receptor forms a complex with gp130, a highly promiscuous cytokine signaling co-receptor essential for various mammalian cell growth and homeostasis pathways. Ligand binding results in signaling through the JAK/STAT and MAPK pathways.

►Neurotrophic Factors in Nerve Regeneration

Cingulate Cortex – Role in Eye Movements

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Definition

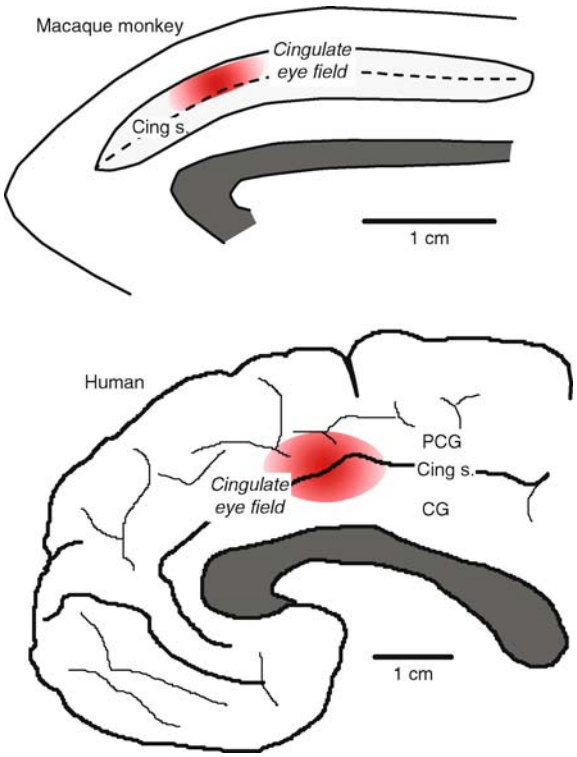
Cingulate cortex, occupying the gyrus and surrounding cortex encompassing the corpus callosum includes a variety of areas with diverse functions.

Characteristics

Higher Level Structures and Lower Level Components

Traditionally regarded as part of the limbic system, the cingulate cortex is a large and heterogeneous part of the cerebral cortex that can be partitioned based on architecture, connectivity and functional properties [1,2]. First, cingulate cortex is divided into a posterior part (Brodmann's area 23) and an anterior part. The anterior cingulate cortex can be divided into a ventral zone (occupying the surface of the cingulate gyrus, containing Brodmann's areas 24a, 24b and the subcallosal area 25) and a dorsal zone (mainly in the cingulate sulcus, containing Brodmann's areas 24c and 32). In humans, this functional area often extends into the surrounding paracingulate gyrus.

A putative cingulate eye field has been described in the caudal portion of anterior cingulate cortex (Fig. 1), and visual and saccade-related activity has been described in a portion of posterior cingulate cortex (not shown). Anterior cingulate cortex can contribute indirectly to ocular motor function through dense, reciprocal connectivity with the supplementary eye field and a weaker linkage with the frontal eye field, superior colliculus and ocular motor thalamic nuclei [3].

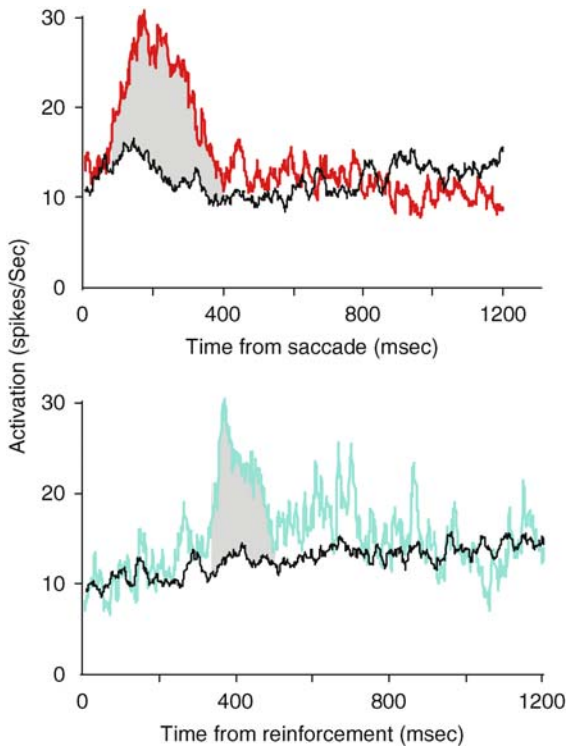


Cingulate Cortex – Role in Eye Movements.
Figure 1 Medial view of macaque monkey (*top*) and human (*bottom*) brains showing estimated location of zone in cingulated cortex related to movements of the eyes. Abbreviations: *CG*, cingulated gyrus; *cing s*, cingulate sulcus; *PCG*, paracingulate gyrus.

Higher Level Processes and Lower Level Processes

Neurons in posterior cingulate cortex of macaque monkeys discharge in response to visual stimuli and following saccadic eye movements [4], and functional imaging in humans has described activation in posterior cingulate cortex associated with visually guided saccades [5]. However, more evidence indicates a role in gaze control for a caudal zone in anterior cingulate cortex. Saccadic eye movements can be evoked by electrical microstimulation of a region in the upper bank of the cingulate sulcus directly ventral to the SEF, in area 24c [6]. Functional brain imaging studies have reported activation in anterior cingulate cortex during production of self-generated saccades guided by arbitrary cues [7].

In macaque monkeys performing a task that requires inhibition of a partially prepared movement in response to an imperative stop signal, neurons in anterior cingulate cortex were modulated following errors or when reinforcement was earned but not delivered (Fig. 2) [8].



Cingulate Cortex – Role in Eye Movements.
Figure 2 Monitoring signals in anterior cingulate cortex. Activity of a single neuron is shown aligned on the time of a saccade (*top*) or time of reinforcement (*bottom*) on trials when the saccade was correct and earned reinforcement (black), when the saccade was an error and received no reinforcement (red), and when the saccade was correct but reinforcement was not delivered (blue). This representative neuron signaled the unexpected absence of reinforcement.

This signal from single neurons corresponds to a scalp potential referred to as the error-related negativity, which may originate from a single dipole in anterior cingulate cortex. In addition, a diversity of neurons in anterior cingulate cortex signal when reinforcement is earned and received, earned and not received, or delivered but not earned. The activation of these neurons can guide adjustments of performance, probably derived from signals arriving from brainstem dopamine neurons, the ventral striatum or orbital frontal cortex. These results are consistent with a body of research indicating that anterior cingulate cortex monitors performance for executive control.

Function

Three general perspectives have framed hypotheses about the function of cingulate cortex: motor control, performance monitoring and motivation. Cingulate cortex seems to contribute indirectly to gaze control through mediating the influence of motivation derived from the consequences of previous actions.

Pathology

Damage to cingulate cortex in humans results in diverse disorders. Lesions focused in a limited part of anterior cingulate cortex result in impairments in producing memory-guided saccades and antisaccades [9]. These deficits involved impaired suppression of reflexive saccades as well as increased latency of visually guided saccades.

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Cingulate Gyrus

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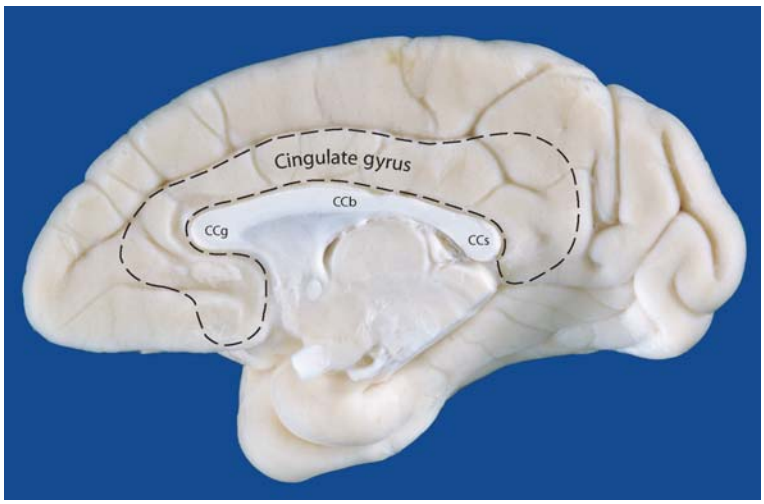
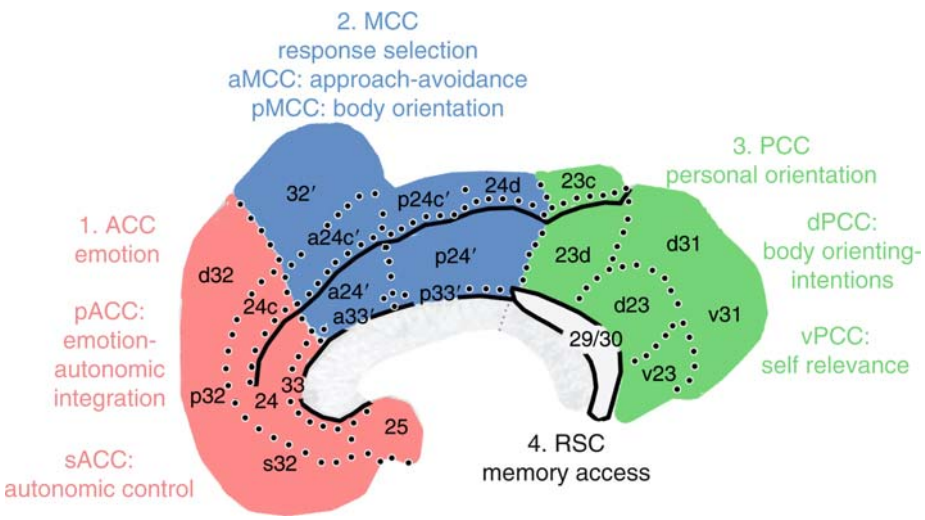
Definition

The cingulate gyrus is a prominent part of the cerebral cortex on the medial edge of each cerebral hemisphere (Fig. 1).

It is dorsal to the body of the corpus callosum and wraps around the genu of the corpus callosum rostrally and the splenium caudally. The cingulate gyrus is an integrative premotor structure that participates in remembering and predicting outcomes and, where necessary, generating behaviors to integrate autonomic and ▶skeletomotor outputs for specific environmental contexts. Structural and functional observations show this cortex is organized into four regions [1], an anterior cingulate cortex (ACC), a midcingulate cortex (MCC), a posterior cingulate cortex (PCC) and a retrosplenial cortex (RSC) (Fig. 2).



Cingulate Gyrus. Figure 1 Medial surface of the monkey (Macaca mulatta) cerebral hemisphere showing the cingulate gyrus (*outlined by the dashed line*). Abbreviations: *CCb, CCg, CCs*, body, genu and splenium of the corpus callosum, respectively.



Cingulate Gyrus. Figure 2 The four region neurobiological model of cingulate cortex is based on interdisciplinary observations in cytology, connections, functions and disease vulnerabilities. This overview of the four regions is plotted onto a flat map of human cingulate cortex such that areas in the cingulate and callosal sulci can be shown. The *thick black lines* are the dorsal and ventral apices of the cingulate gyrus and the retrosplenial cortex (*RSC*) is in the depths of the callosal sulcus. The *dotted lines* separate each cytoarchitectural area. In consonance with the regional designations, some areas are subdivided further; *ACC* into subgenual *s* and pregenual *p*; *MCC* into anterior *a* and posterior *p*; *PCC* into dorsal *d* and ventral *v*. The rationale for each region and subregion is detailed in Chapter 1 of *Cingulate Neurobiology and Disease* [11].

These four regions serve as the basis for evaluating cingulate functions and vulnerability to particular diseases.

Characteristics

Regional Structure and Functions

The ACC is involved in assessment of valenced information and the long-term storage of emotional objects and events and contributes to tonic mood states (Fig. 2). It appears to separately store happy events rostrally in area 32 and sad events caudally in areas 24 and 25. The ACC receives a massive input from the amygdala and a link between emotion and ►autonomic regulation occurs in area 25 in the subgenual ACC which projects to autonomic regulatory sites including the hypothalamus, periaqueductal gray and parabrachial nucleus. The highest concentration of cingulate glutamate receptors is in the ACC. There are proportionately fewer γ-aminobutyric acid (GABA) receptors, which are higher in the PCC [2].

The MCC coordinates decision-making about behavioral outcomes in a number of ways, i.e., anticipation of outcomes, comparing actual with expected outcomes and modifying behaviors as rewards are reduced [3]. In view of its prominent role in both rewarded and aversive (i.e., painful) outcomes, it is not surprising that an important feature of this region is the two cingulate premotor areas located along the cingulate sulcus that regulate skeletomotor outputs (Fig. 2). Both cingulate motor areas have extensive motor system projections that include the frontal cortical motor areas and subcortical structures. Important subcortical projection targets include the putamen, red nucleus, pontine nuclei, facial motor nucleus and spinal cord [4].

The anterior and midcingulate regions have high densities of dopaminergic inputs and D1 receptors. The anterior MCC appears to have the highest such innervation in the cingulate gyrus and, in view of the interactions with reward centers such as the nucleus accumbens, it is likely that the MCC in particular is involved in selecting among rewarded outcomes.

The PCC and RSC are adjacent to one another on the posterior cingulate gyrus, but they differ considerably in their structural organization including cytology and circuitry and contribute to memory and visuospatial functions (Fig. 2). The ventral subdivisions of these two regions are involved in assessing self-relevant sensory information, storing self-relevant memories and in making this information available for ►premotor processing and decision making in the ACC and MCC. Acetylcholine is a modulatory neurotransmitter in high concentrations in the PCC. GABA receptors, which regulate a chloride conductance and are the chief inhibitory neurotransmitter in the central nervous system, are in highest concentration in the PCC [2].

Sensory Integration Function

Medial Pain System

The MCC is one of the most frequently activated cortices during noxious ►cutaneous stimulation that generates the conscious perception of pain and is a critical component of limbic structures that form the medial pain system [5]. This system is involved in the emotional and motivational (premotor) aspects of pain processing and anticipation of pain. In contrast, the primary role of the lateral pain system is in the localization and intensity coding of ►noxious stimuli. The nociceptive signal to the medial pain system/cingulate cortex arises from the midline, mediodorsal, and intralaminar thalamic nuclie and results in large receptive field organization. This region in turn, projects to the midbrain periaqueductal gray, which regulates many emotional expressions as well as the descending noxious inhibitory system. Functional imaging studies show that the ACC and MCC respond to both ►visceral and cutaneous ►noxious stimuli. While the visceral responses predominate in the ACC, cutaneous related, nociceptive responses predominate in the MCC. The ACC is thought to mediate the affective component of pain. Neurons in the ACC respond to multiple forms of noxious ►cutaneous stimuli irrespective of somatotopic origin [6] and the site of nociceptive visceral activation in this region overlaps with the site generated during the anticipation of noxious visceral stimulation. Innocuous distension in contrast has no such effect. The MCC is involved in pain ►avoidance behaviors and both the ACC and MCC are active when anticipating pain and may code for the relative intensity of noxious stimulation even though this is not their primary role in pain. Finally, the highest density of mu-opioid receptors in the brain is in ACC and the opiate placebo is associated with activation in this region.

Visual and Spatial Integration

The PCC receives extensive sensory inputs from parietal, temporal and occipital cortices as well as from the thalamus, including the pulvinar nucleus. Such information is employed in orientation of the head and body to sensory stimulation, orientation in larger (allocentric) spaces and in processing large scale/whole visual field information (Fig. 2). The dorsal PCC is involved in body orientation in space and its structural and functional relationships with the caudal cingulate motor area of the MCC may contribute to movement associated with visuospatial stimuli. The ventral PCC monitors self-relevant information and engages in self-reflection and context dependent sensory processing. Such information from sensory afferents enters the cingulate gyrus for processing via connections with the ACC that determine which information is particularly relevant to current needs and will be used

to guide premotor processing in other parts of the cingulate gyrus [7].

Regional Disease Vulnerabilities

Impaired neuronal processing in the cingulate gyrus has been implicated in the symptoms of many neuronal diseases. To some extent each region is vulnerable to different types of disease insults. Clinically, the ACC is vulnerable to major depression during which volumetric reductions have been noted along with reductions in glucose metabolism. Intracranial electrical stimulation of this structure in drug resistant depressed patients significantly reduces symptom expression [8]. Additionally, structural changes have been associated with alterations in the serotonin transporter gene and one of the primary sites of clinical efficacy for selective serotonin reuptake inhibitors (SSRIs) is in the ACC. In the light of the relatively high concentrations of serotonin 1A receptors in the ACC, there is yet another reason for considering this to be the site of symptom resolution over the course of SSRI treatment.

Many movement disorders are related to disruption of processing in the MCC. Obsessive-compulsive disorder is associated with various forms of repetitive behaviors including hoarding and cleaning and with high levels of activity in the MCC. The role of the MCC in this disorder is emphasized by the fact that neurosurgical midcingulate ablations can abolish such behaviors. Attention deficit/hyperactivity disorder is another movement disorder and it has been shown that the anterior MCC is reduced in volume in this disorder and that cognitive processing is altered in this region as well. Finally, since there is a high level of nociceptive activation of the anterior MCC and hypnosis modulates activity in this region, hypnosis can be used to induce sedation for surgical procedures that employ only local anesthetics [10].

A number of disorders have a reciprocal influence on activity in the ACC and the MCC. Thus, irritable bowel syndrome is associated with reduced activation in the ACC (where visceral nociceptive information is normally processed) accompanied by enhanced processing in the anterior MCC. This heightened activity could result from anticipatory processing associated with bowel symptoms and premotor activity required to resolve intrusive bowel habits. It is an interesting fact that the anterior MCC is also active during micturition in healthy subjects and urinary incontinence accompanies anterior cingulate trauma. Thus, decision-making about the appropriate context for bowel habits may be guided by the MCC.

It is well known that the PCC is involved in Alzheimer's disease, in many instances quite early in symptom expression. Some cases of mild cognitive impairment have been shown to progress to Alzheimer's disease and the first site of damage in some cases is in the dorsal PCC and RSC [9]. Thus, early signs of memory and visuospatial impairment may be mainly due to damage in the posterior cingulate gyrus rather than solely a product of medial temporal lobe damage as is often assumed.

A current and general reference on the structure, circuits, functions and diseases of the cingulate cortex will be available in 2008 titled *Cingulate Neurobiology and Disease* (Oxford University Press). The four regions of cingulate cortex are very important to the clinical diagnosis of many psychiatric diseases and the selective vulnerabilities of cingulate regions validate the four region neurobiological model. In the future, treatments for many neurological and psychiatric diseases will employ pharmaceutical and behavioral strategies to target the cingulate gyrus.

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Cingulate Motor Areas

Definition
Secondary motor areas located in the cingulate gyrus of the frontal lobe in the medial wall of the cerebral hemisphere. Three cingulate motor areas have been identified and all contain corticospinal neurons.

►Corticospinal Neurons
►Motor Cortex: Output Properties and Organization

Cingulate Sulcus

Synonyms
Sulcus cinguli; Cingulate sulcus

Definition
A sulcus visible in median section, which surrounds the cingulate gyrus and thus encloses the limbic lobe. In the transitional region between occipital lobe and parietal lobe it joins the marginal part and ascends to the margin of the hemisphere.

►Telencephalon

Cingulum

Definition
The cingulum is a strong bundle of association pathways of varying length that connects different cortical centers of a hemisphere. It is situated on the lower margin of the cingulate gyrus.

►Telencephalon

Circadian Activity

Definition
Activities with an endogenous period of about 24 h, of about a day. Such rhythms are seen in all living organisms, including plants, animals, fungi and cyanobacteria. These rhythms are not driven by or dependent upon stimuli in the external world, but instead, they persist in constant conditions. Circadian activities have the same period over a range of temperatures (i.e., they are temperature compensated), and are largely resistant to metabolic changes that might influence rhythmic activity that might result from high or low temperatures.

External stimuli can however, reset the phase (or start time) of a circadian rhythm.

►Circadian Rhythm

Circadian Clock Genes

►Clock Genes

Circadian Cycle

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Definition
The sequence of molecular, biochemical, physiological and behavioral changes that occur over the course of a single near-24 h period within an organism.

Characteristics
A circadian cycle defines the sequence of molecular, biochemical, physiological and behavioral changes that occur over the course of a single near-24 h period within an organism. Presumably, these characteristic near-24 h temporal programs represent an adaptation to existence on a planet where the repetitive cycle of light and darkness may well be the most ancient and most persistent event under which all life has evolved. The fundamental nature of these 24-h rhythms is evident from their wide range of expression; they are present in organisms across all phyla. Circadian ►oscillations in organismic physiology and behavior allow anticipation of daily environmental change. The capacity to anticipate, and subsequently, to prepare for change promotes reproductive fitness, thereby enhancing survival of the species.

Importantly, this periodicity is present under unchanging, or constant, environmental conditions, which demonstrates that the oscillation represents a program that is endogenously generated. Circadian cycles can be

slightly longer or shorter than 24 h, depending on the organism. For example, most strains of mice exhibit a ►rest/activity cycle that is slightly shorter than 24 h, whereas hamsters display a rhythm that is slightly longer than 24 h. Although rest/activity cycles are a commonly studied expression of the circadian cycle in animals, similar oscillations can be observed in hundreds of other biological events, ranging from the level of whole organism behavior to gene expression. The fungus, *Neurospora crassa*, rhythmically produces asexual spores with a period of 22 h under ►constant conditions, including constant darkness (DD) [1]. Leaf movements in plants were among the first circadian oscillations to be recorded. Photosynthesis, opening of stoma and growth are all circadian controlled phenomena in plants. The prokaryotic cyanobacterium, *Synechococcus*, uses the 24-h cycle to separate the process of nitrogen fixation from photosynthesis. At the molecular level, the cycle is defined by a single revolution of the interlocking feedback loops that comprise the core molecular clock machinery [2]. A primary function of the cycle is to allow synchronization between the organism and the recurrent environmental sequence of light and darkness. Thus, the cycle is typically divided into subjective day and subjective night. ►Subjective day may be defined as the sequence of events that occur during the lighted portion of a typical 24-h period. Likewise, ►subjective night may be defined as the sequence of events that occurs during the dark portion of a typical 24-h period.

Characteristics of the Circadian Cycle

Across all phyla, circadian cycles are characterized by several common features. The self-sustained oscillation is always close to, but not necessarily exactly, 24 h in duration, and can be adjusted in response to environmental changes. These oscillations persist when the organism is placed into constant environmental conditions, which expose the endogenous nature of the rhythm. Although historically these rhythms were first investigated at the level of the whole organism, rhythms are expressed in organs, tissues and even in cells cultured *in vitro*. Perhaps the most studied example of this is the firing rate rhythm of the mammalian ►suprachiasmatic nucleus (►SCN). Hypothalamic brain slices containing the SCN, the home of the primary clock in mammals, exhibit ►self-sustained circadian oscillations in the neuronal ensemble firing rate, metabolic glucose uptake and clock gene levels [3]. More recently, persistent rhythms in other mammalian tissues, as well as in dissociated body parts in *Drosophila melanogaster*, and finally, in dissociated cells, including rat fibroblasts.

Perhaps the most important attribute of the circadian cycle is its ability to adjust in response to environmental change. Although periodicity is determined by placing the organism in constant conditions, life transpires under conditions of cyclic environmental change. Although the circadian cycle is temperature compensated, meaning that it runs with a constant periodicity through a wide range of temperatures, temperature cycles of 24-h duration can be used to set the phase of the cycle. Many other cyclic environmental conditions, such as food availability, presence of predators, and, most importantly, light, can also act as ►zeitgebers for circadian cycles. Zeitgebers mimic the cycle formed by the earth's rotation, and can entrain the circadian cycle such that physiological and behavioral activities are synchronized with the environmental cycle of light and darkness. This active adjustment of the circadian cycle by zeitgebers is termed ►entrainment.

Biochemical Time Zones

The internal circadian cycle is a series of programmed biochemical events that occur in a defined sequence. The cycle is sensitive to external stimuli, which can act to adjust the internal workings of the clock to synchronize with the environment. The cycle is, however, differentially sensitive to stimuli. Certain stimuli only affect the cycle during the clock's subjective night, whereas others are restricted to access the clock during the day. Generally, if a particular stimulus might be perceived as an error signal at a given position within the cycle, it is that time that the cycle is sensitive to change in the presence of that signal. Light, for example, will only act to adjust phase during the portion of the cycle where light would not be expected to be present. Thus, the clock itself, temporally defines, or gates, the information that can access the timekeeping mechanism. The clock itself opens and closes gates as the circadian cycle progresses. Although the filter changes fluidly over the course of the cycle, sets of specific time domains, or phases have been identified.

In the SCN, each time domain is characterized by the activation of specific signal transduction pathways. Generally, ►gating of the SCN circadian cycle is divided into four domains, day, night, dusk and dawn [3]. Dusk and dawn, which are the periods that encompass the transition periods between the day and night time domains, are similar. These periods are characterized by sensitivity to phase ►resetting in response to ►melatonin, a hormone used to measure day length, via essential activation of protein kinase C-dependent signal transduction pathways. The daytime domain is sensitive to phase adjustment by stimuli that act through cAMP and cAMP-dependent protein kinase. Generally, ►serotonin and ►pituitary adenylyl cyclase activating peptide (►PACAP) are neurochemicals known to act through cAMP-dependent mechanisms to alter clock function during the daytime domain.

The nighttime domain is perhaps the most complex. The gates for adjustment in response to cAMP dependent pathways are closed. Opened are two distinct gates. A pathway that responds to cholinergic stimulation, which may be involved in circadian regulation of sleep and wakefulness, can access the timekeeping mechanism through elevation of cGMP and activation of cGMP-dependent protein kinase. In addition, at night the clock is sensitive to pathways activated by environmental light, acting through glutamatergic neurotransmission. Influx of calcium and nitric oxide production are characteristic of light-signaling.

Temporal restriction of sensitivity to exogenous signals is fundamental to maintaining synchrony of the circadian cycles with the environment. Internal gating within the clock itself allows the clock to anticipate environmental change. This ensures that the individual can maintain synchrony with a constantly changing external environment.

Molecular Building Blocks

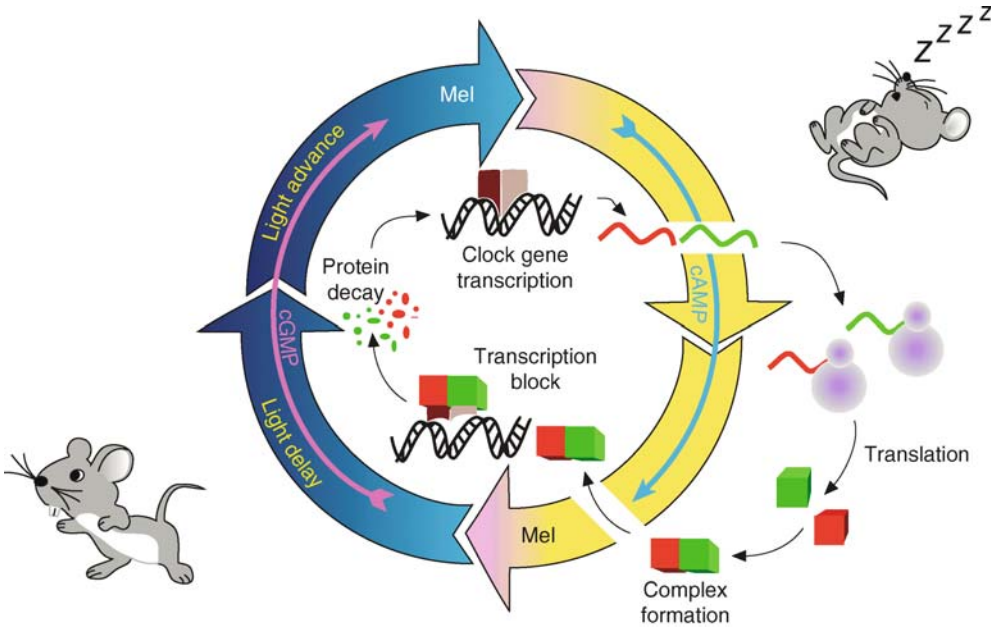
Although organismic rhythm generation is likely an emergent property of a complex system, the source of the circadian cycle lies within individual cells. The search for a genetic basis for the circadian cycle began early in the last century with the selection of bean plants for breeding based upon expression of long or short periods under constant conditions. The first "clock" gene, (►Period, *Per*) was discovered in *Drosophila melanogaster* using mutagenesis screens [4]. Shortly thereafter, a similar approach led to discovery of the Frequency (*Frq*) gene in *Neurospora crassa* [5]. The 1990s were witness to a ►clock gene "explosion," distinguished by the discovery of numerous core components of the machinery that drive circadian cycles, in many model organisms, including mice, humans, frogs, plants, fungi and cyanobacteria.

Sequence analysis has determined that there is little similarity among proteins that form clock components across the major phyla. However, the genetic basis for generation of a circadian cycle in all organisms studied to date is a functional transcriptional/translational feedback loop(s) (Fig. 1). In its simplest form, the cycle is generated by transcription of a gene, translation of the transcript into a protein product, followed by negative feedback, whereby the protein product or one of its downstream targets, returns to inhibit further transcription of the gene. Release of the negative feedback requires degradation of the protein product, which allows the cycle to begin again. Thus, many of the core "clock" genes are circadian-controlled transcription factors. Rhythmic transcription leads to rhythmic production of proteins. The *Per* genes of *Drosophila* and mammals are examples of transcriptionally regulated clock components. Rhythmic control of transcription is not, however, the only source of rhythmic protein formation. Evidence suggests that regulation of translation initiation may be important for the *Neurospora* clock gene, *Frq*.

More recent studies suggest that rhythmic transcription is not required for generation of a circadian cycle. Circadian oscillations can be generated in a test tube containing just three cyanobacterial proteins and ATP [6]. The observed oscillation, which was rhythmic phosphorylation of the *Synechoccus* protein KaiC, was robust and temperature compensated. These studies suggest that a metabolic oscillator, independent of the transcriptional/translational feedback loop, generates the circadian cycle. Whether this is a unique feature of the cyanobacterial clock, or a general principle that pertains to construction of circadian clocks, remains to be determined. It is possible that the circadian cycle results from complex interactions between two oscillators, one formed by the genetic component expressed as the transcriptional/translational feedback loop, and a second derived from a metabolic oscillator.

Although the mechanism for forming a cycle can be relatively simple, making the cycle repeat with 24-h periodicity is the source of complexity. A simple feedback loop can be completed in as little as 3 h. Multiple interlocking feedback loops and posttranslation modification of protein products (similar to that described above for cyanobacteria) are important for generation of the circadian cycle in multicellular organisms. Despite more than a decade of research in this area, the molecular details of generating a clock that measures time on a 24 h scale are still relatively unclear.

In mammals, the protein products of the ►*clock* (*Clk*) and ►*Brain muscle ARNT-like1* (►*Bmal1*) genes heterodimerize through interactions of PAS domains to form a complex that binds to e-boxes in the promoters of target genes. The *period* (*Per*) and ►*cryptochrome* (*cry*) gene promoters are clock-relevant targets of CLK:BMAL1-driven transcription. As PER and CRY proteins accumulate, they form multimeric complexes that enter the nucleus and inhibit CLK:BMAL1-mediated activity, effectively blocking their own transcription. A key element of the PER/CRY feedback component is a delay in the accumulation of PER proteins by about 6-h, relative to the mRNA levels. This is likely that posttranslational modification, such as phosphorylation of PER plays an important role in regulating the accumulation, activity and/or subcellular localization of the protein. Similar events regulate the FRQ protein in *Neurospora.* At the end of the circadian cycle, PER proteins are targeted for degradation, which releases the repression of transcription, thereby allowing the initiation of a new biological day. This primary loop is stabilized by activities of orphan nuclear receptors ►Rora and Rev-Erbα, which activate and repress *Bmal1* expression, respectively. CLOCK:BMAL heterodimers activate ►*Rev-Erbα* by binding to ►E-box



Circadian Cycle. Figure 1 The circadian cycle is a sequence of molecular, biochemical, physiological and behavioral changes that occur over the course of a single near-24 h period within an organism. The left side of the diagram depicts events that occur during the night, whereas the right side depicts events occurring during the day. The nocturnal mouse spends more time sleeping and resting during the day, and shows increased activity levels during the night. Transcription of negative elements of the clock's feedback loop is initiated in the nucleus (represented by the inner part of the circle) during the late night and proceeds into the first half of day. Transcripts are transported into the cytoplasm where translation occurs at ribosomes. Proteins accumulate during the late part of the day and into the early night. Protein complexes form and re-enter the nucleus, where they act to inhibit their own transcription. Mid to late night is marked by degradation of the proteins, which releases transcriptional repression and allows the cycle to repeat. Also depicted on the diagram are times when the clock mechanism is subject to resetting by specific signaling molecules. During the day, clock resetting occurs primarily through signals that activate cAMP. In contrast, night is dominated by resetting in response to cGMP. Light can reset the clock throughout the night, causing phase delays during early night and phase advances during late night. The clock is also sensitive to resetting in response to melatonin (Mel), with windows of sensitivity occurring at dusk (day-to-night transition) and dawn (night-to-day transition).

elements in its promoter, and Rev-Erbα subsequently feeds back to attenuate *Bmal1* transcription. Rora is necessary for normal expression of *Bmal1* and consolidation of locomotor activity [7].

Circadian Cycle in Disease

Studies of animals bearing mutations in their circadian cycle are revealing new information regarding the importance of circadian clocks in health and well-being. In humans, mutations of the Per genes lead to abnormal sleep patterns, such as seen in Advanced phase sleep disorder. Per1 and Per2 mutant mice have increased risk of multi-site carcinogenesis [8]. Clock mutant mice develop obesity [9]. Although the relationship between the circadian cycle defects and development of pathologies remain unclear, it is certain that clock defects can lead to health problems. The importance of the circadian cycle is health is only beginning to be appreciated.

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Circadian Desynchronization/ Circadian Desynchrony

►Circadian Sleep Phase Syndromes

Circadian Food Anticipatory Activity (FAA)

►Food Entrainment

Circadian Output Genes

►Clock-Controlled Genes

Circadian Pacemaker – Temperature Compensation

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Definition

One of the defining characteristics of circadian pacemakers and indicates the independence of the speed of circadian clock processes of environmental temperature. Mechanisms involved, so far not elucidated in full detail, entail at least two processes that are similarly affected by temperature changes, but with an opposing and counterbalancing effect on the periodicity of the clock system. As a result of temperature compensation, the increase in reaction velocity for every 10° rise in temperature (►Q_{10}) of processes governed by ►circadian pacemakers reaches values of about 1.

Characteristics

The Phenomenon

The first study on temperature independence in circadian timing was published in 1932 [1], showing the precision in time memory of foraging bees in spite of changes in environmental temperature. The early notion that the velocity of circadian processes does not vary with environmental temperature (within certain ranges) has been based on experimental evidence from a wide variety of sources. Evidence for temperature compensation of circadian rhythms has been collected for luminescence rhythms in unicellular algae, daily leaf movements in plants, and locomotor activity in cockroaches and lizards (as compiled in [2]). Comparisons of ►period length, expressed as Q_{10}, the quotient of reaction rates per 10°C, revealed Q_{10}s in the range of 0.9–1.2 [3]. This is in sharp contrast to the usually temperature-dependent kinetics of biochemical processes resulting in Q_{10} values of roughly 2–3 [4]. These findings, together with the insight that a functional clock subject to temperature dependence would be prone to inaccuracy in the natural environment, caused Pittendrigh to list temperature compensation as item XI on his famous list of 16 empirical generalizations about circadian rhythms [3]. Since then, a vast literature on circadian Q_{10} values has accumulated, confirming early observations. Recently, temperature compensation has been demonstrated in ►clock gene expression rhythms in mammalian fibroblast cultures [5]. Also the phosphorylation rhythms of the Cyanobacterial protein KaiC *in vitro*, in the presence of two other proteins but in absence of transcription and translation, shows temperature compensation, in the range of 25–35°C [6].

Mechanism

A simple model for temperature compensation has been based on two chemical reactions, both of which are temperature-dependent. The rate of the first reaction may control period length, whereas the product of the second reaction would inhibit the first reaction. With such a model, Q_{10} values slightly smaller than 1 also can be explained [7]. Temperature compensation also is an important aspect of neuromodulation (e.g., motor networks), and here again the intrinsic temperature dependences of the processes that contribute to the system output can simply balance each other because reaction rates have been "chosen properly" [8].

Alternatively, the structure of the network itself can stabilize its output, as also has been suggested for networks in clock systems, emphasizing pathway phenomena rather than results of single enzyme properties [9]. The hunt for molecular key players in the process of temperature compensation has nevertheless started, as illustrated in a study on the role of specific core clock proteins in Arabidopsis [10].

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Circadian Pacemaker Neuron

Definition

Circadian rhythms of animal behavior and physiology are coordinated by a master clock in the central nervous system of each individual. This master clock comprises a collection of multiple circadian pacemaker neurons.

Each pacemaker neuron has the capacity for autonomous circadian oscillation of cellular parameters such as gene transcription and action potential firing rate. Pacemaker neurons communicate circadian phase information to one another – for the purpose of synchronizing or otherwise coordinating their autonomous rhythms – and to downstream neural targets – for the purpose of driving overt behavioral and physiological rhythms. This communication of phase information occurs via both classical synaptic neurotransmission and the release of peptide neuromodulators.

►Cellular Clock
►Circadian Rhythm
►Human Circadian Timing System
►Morning/Evening Oscillators

Circadian Rhythm

Definition

A circadian rhythm is a biological oscillation that has a frequency of about once per 24 h when conditions are constant (e.g., when removed from regular, 24 h daily cycles of the environment, such as light and dark or warm and cold). The word "circadian" is derived from circa dies, Latin for "about a day." Circadian rhythms are synchronized to exactly 24 h under natural conditions by zeitgebers, with light acting as the major synchronizing agent.

►Chronobiology
►Entrainment
►Human Circadian Timing System

Circadian Rhythm Sleep Disorders

►Circadian Sleep Phase Syndromes

Circadian Rhythms of Autonomic Functions

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Synonyms

Circadian rhythms are all biological rhythms that express themselves with a rhythm of ~24 h.

Autonomic functions are all processes that are not voluntarily controlled and are executed by the brain via nerve fibers of "the autonomic nervous system" that target our organs.

Definition

Autonomic nervous system is that part of the central nervous system that operates outside our voluntary control. The executing branches of the autonomic nervous system form a parasympathetic or a sympathetic branch. These two branches, in general, target structures and organs in the body and have an antagonistic function whereby it is assumed that the parasympathetic branch is involved in anabolic functions and the sympathetic branch in catabolic functions.

Characteristics

Origin of Circadian Rhythms

The suprachiasmatic nucleus (SCN) is a small brain structure of ~60,000 neurons located on the top of the optic chiasm. Light input reaches the SCN via retinal fibers that terminate in the ventral part. Many individual neurons of the SCN have their own rhythmicity of electrical activity whereby electrical activity and relative inactivity occur with a frequency of about 24 h. The SCN has been shown to be responsible for generating all rhythmicity in mammals; without SCN, no endogenous rhythmicity can sustain. The output of the biological clock transmits its endogenous rhythmicity to the brain and the rest of the body via its projections to hypothalamic target structures. In addition, transfer of its information, especially to generate behavioral activity, may occur by diffusible substances [1]. However, the presence of precise anatomical connections and the presence of locally acting (amino acid) neurotransmitters in SCN projections make it likely that large part of SCN information will be transmitted via precise anatomical connections.

Anatomical studies showed that the SCN uses at least four different types of neuronal targets in the hypothalamus to pass on its circadian signal: (i) endocrine neurons, (ii) autonomic neurons located in the paraventricular nucleus of the hypothalamus (PVN), (iii) hypothalamic structures that may dissipate the circadian signal to brain regions within and outside the hypothalamus, (iv) areas outside the hypothalamus (Fig. 1).The connection from the SCN to the ventrolateral preoptic nucleus is important for the induction of sleep. It is not clear at present how and where the SCN may synchronize other behaviors such as food intake and locomotor activity.

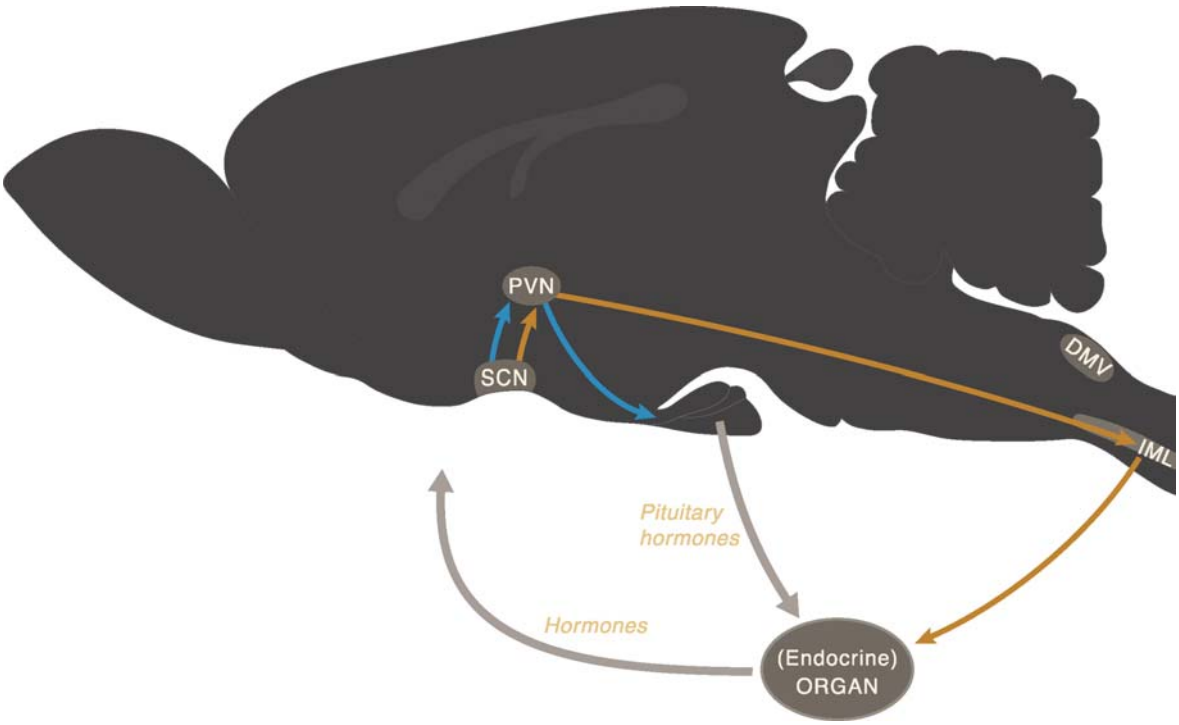
Here, special attention will be given how the SCN targets the body via the autonomic nervous system. It is unmistakable, however, that this action on the autonomic nervous system cannot be viewed independently from the way the SCN affects the hormonal systems of the body. For many hormones, it holds that they are released with a circadian pattern; responsible for this is the SCN that influences neuroendocrine neurons or the endocrine organs or both.

SCN-mediated control of the melatonin surge indicates that control of hormone secretion via the autonomic nervous system is an important aspect of SCN function. In addition, a pronounced circadian change in the sensitivity of the adrenal cortex to ACTH has been demonstrated since long. Transneuronal tracing and physiological experiments provided proof that, apart from the classical neuroendocrine control of the adrenal cortex by the PVN-CRH-ACTH-cascade, an important neuronal SCN-PVN-sympathetic-adrenal cortex link also determines the final corticosterone secretion from the adrenal. Thus, the SCN utilizes a dual mechanism to organize an optimum secretion of corticosterone not only via direct control of the hypothalamic neuroendocrine (CRH) neurons but also via control of autonomic motor neurons. We propose this as a general principle that holds not only for endocrine glands but also for other organs [2]. For example, recent evidence indicates that just before onset of activity, the SCN not only increases insulin sensitivity, resulting in a physiological meaningful increased uptake of glucose in muscle tissue but also causes increased hepatic glucose production at the same moment.

This evidence warrants a closer look at the possibility that the SCN controls the organs of our body.

SCN Prepares the Body for Changes in Activity

The influence of the SCN on hormonal secretion seems to be one of the important routes by which the SCN may affect the body. This conjecture is enforced by the fact that the secretion of several hormones is influenced or even completely regulated (melatonin) by the SCN. A number of anatomical and physiological studies clarified that the SCN affects melatonin secretion by inhibiting its secretion by GABA and stimulating its secretion with glutamate at the level of the preautonomic neurons of the PVN. However, it does not seem very likely that other organs are affected via the same sympathetic branch. In humans, for example, the moment of melatonin secretion is also the moment for sleep, not the best moment to activate indiscriminately the whole sympathetic system because just before sleep, e.g., the heart rate needs to slow down instead of going up. In fact, the autonomic output to our organs is even further differentiated: anatomical evidence has shown that not only separate sets of neurons in PVN and SCN control parasympathetic and sympathetic motor neurons in brain stem and spinal cord, respectively, but also separate neurons affect different organs. This provides the anatomical basis to allow the SCN to influence both autonomic branches at the same time in an opposite manner. This is illustrated by the fact that while the sympathetic input to the pineal is increased for melatonin secretion, the sympathetic input to the heart



Circadian Rhythms of Autonomic Functions. Figure 1 The main pathways by which information from the SCN is transmitted to the body, mainly by the PVN via hormonal and autonomic signals. These signals, hormonal, parasympathetic, and sympathetic, reach peripheral organs ranging from adrenal gland and liver to fat tissue and gonads. From these organs, both visceral sensory and hormonal information will reach the hypothalamus. These connections provide the hypothalamus with unique information that allows the organism to adjust and balance both peripheral light/dark information and the metabolic information from the peripheral organs.

is lowered to allow the heart to beat slower. Other studies indicate that already before an animal becomes active its physiology is changed such that the animal is optimally prepared for activity. These changes are largely mediated by the autonomic nervous system.

Furthermore, the rhythmic secretion of corticosterone (cortisol in humans) is primarily driven by the SCN; lesioning the SCN removes the daily corticosterone increase, just before the active period, completely. Clearly, other stimuli also affect corticosterone secretion, e.g., disturbing events (stress) that take pace in the environment of the animal still increase corticosterone in SCN-lesioned animals; in fact, the animal even responds with much higher corticosterone secretion to stress after SCN-lesioning, indicating that the SCN plays an important role in inhibiting corticosterone secretion. These observations stimulate the concept that for a normal function of our physiology it is essential that a large number of organ functions are perfectly synchronized and that circadian time, signaled by the SCN, is integrated with all other events that influence behavior or physiological processes. For example, even after fasting for an extended period, the SCN will stimulate an individual to conserve energy during the rest period. It accomplishes that, e.g., by decreasing the set point for body temperature, decreasing glucagon levels, and promoting sleep. Even then, prior to the onset of the activity period, the SCN will initiate the processes to prepare for activity (e.g., increasing core body temperature and plasma glucose) so that the animal is ready to hunt for food at the end of the sleep.

Another example of how the SCN prepares our body for the upcoming activity by the autonomic nervous system is that it sensitizes our organs for hormones of which the secretion is also influenced by the SCN. An example is the adrenal that just before the onset of the activity period is more sensitive for adreno corticotropin releasing hormone (ACTH). The result of the action of the SCN on the adrenal is that with the same amount of ACTH the adrenal cortex releases more corticosterone at the end of the sleep period than in the beginning of the sleep period. The mechanism for this increased sensitivity is the sympathetic innervation of the adrenal, which is essential for the circadian variation in corticosterone secretion. Signals from the SCN may reach the adrenal via multisynaptic pathways including the PVN and the sympathetic motor neurons located in the intermediolateral column of the spinal cord (IML). This

affects the adrenal such that changes in corticosterone secretion are obtained without any discernable change in ACTH secretion.

Since light is used as a stimulus for the SCN resulting at night in phase shifts and inhibition of melatonin secretion, this stimulus was used to examine the influence of the SCN on the autonomic output of the brain. In (day-active) humans, light exposure resulted in opposite reactions of the autonomic nervous system as compared to the nocturnal rat. Light increased heart rate in humans, as compared to a decrease in heart rate in the rat. Also, these observations fit into the idea that the SCN prepares the individual for the coming activity period and for the coming sleep period and that light, as the signal of the daytime, promotes activity in man and promotes inactivity in rodents.

Similarly we suggest that the SCN – probably by the autonomic nervous system – prepares the muscles for the activity period by increasing their sensitivity to insulin and thus to have a higher glucose uptake. These series of observations have drawn the attention to the capacity of the SCN to change the functionality of our organs not only by the message of hormones but also by affecting the functionality of the organs by the autonomic nervous system.

These examples illustrate one of the main functions of the SCN: preparing the body for the coming activity period. We propose that without this synchronization in physiology, we may have a higher chance to develop diabetes and cardiovascular disease. Consequently, we would like to propose that to live out of synchrony with our SCN would result in the feeling of continuous jet lag or possibly depression. The observation that in depressed persons also a diminished activity of the VP cells in the SCN is observed supports this idea and suggests a possible dysfunction of the SCN in depression.

Autonomic Control of Our Organs

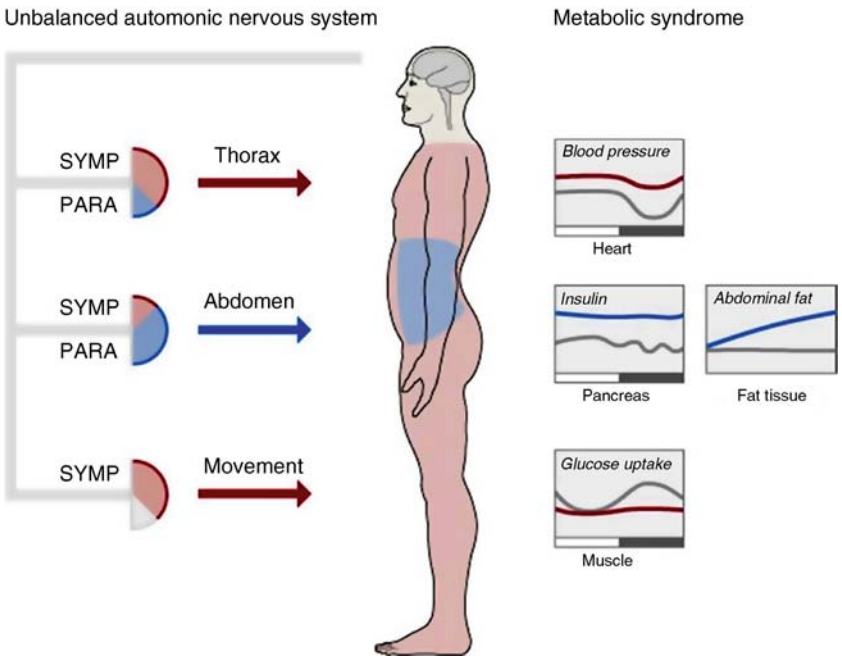
Early studies by Niijima and Nagai [3] showed that autonomic nerve activity is changed after exposure to light while this effect is gone after lesioning the SCN, indicating that light affects the autonomic nervous system by the SCN. Next, PRV tracing techniques showed the SCN to be connected with a large variation of organs, e.g., white and brown adipose tissue, the adrenal, the heart, the liver, ovary, the kidney, and the pancreas. In the hypothalamus and SCN, both parasympathetic and sympathetic preautonomic neurons are differentially connected with these organs of the body. This anatomical framework allows the hypothalamus to affect selectively parasympathetic and sympathetic autonomic output [4].

Consequently, a network is revealed that allows the SCN to communicate its time signal to the body by means of at least three different routes: (i) parasympathetic outflow to the organs, (ii) sympathetic outflow to the organs, and (iii) the secretion of hormones into the circulation (Fig. 1).

An Unbalanced Autonomic Output; Leading to Disease?

Until recently, a number of organs were thought to be excluded from parasympathetic input such as white adipose tissue. However, we obtained evidence for parasympathetic input to white adipose tissue, not only as visceral organ but also as subcutaneous tissue. Parasympathetic input has the function to build up the fat depot while sympathetic input serves to burn fat. This evidence fits quite well with the observations that exercise enhances sympathetic output to the visceral compartment and results in the diminishment of fat stores there. The opposite, a sedentary life style, may result in the accumulation of fat due to a higher parasympathetic and a lesser sympathetic outflow, especially to the visceral fat. Vagal motor neurons in the brain stem that provide input to the subcutaneous fat are completely separated from those that project to visceral fat. At the other hand, the organs in the visceral compartment, such as the liver, pancreas, and abdominal fat, share the same neurons. These observations indicate why an enhanced parasympathetic output to the pancreas after a meal in order to release insulin should also result in an enhanced parasympathetic output to the liver and visceral adipose tissue. In the liver, enhanced levels of insulin from the pancreas will not only stimulate glucose uptake but also the increased parasympathetic input will result in higher glucose uptake and higher storage of glycogen. In the visceral adipose tissue, this combination of enhanced parasympathetic input and elevated insulin levels will result in increased glucose uptake and an accumulation of fat. We propose a hypothesis of autonomic imbalance as one of the possible causes for the metabolic syndrome. A (disturbed) high parasympathetic output to the visceral compartment is the main cause for visceral obesity, hyperinsulinemia, and high levels of FFA. In addition, a simultaneous higher sympathetic output to the muscle and heart compartment would lead to vasoconstriction and hence to insulin insensitivity and hypertension (Fig. 2).

The fact that also the PVN and SCN show this division in projections fits well in our hypothesis that food abundance and the major change in lifestyle in the western world resulting in inactivity during the active period, and enhanced food intake and activity in the rest period (shortened sleep period) may not only affect our daily activity and food pattern but may also lead to a disturbed balance in the hypothalamus. Thus, the biological clock is getting the wrong type of signals across the 24-h period, resulting in general in a flattened rhythm output. One of the major effective treatments of the metabolic syndrome, that is, enhanced activity during daytime together with a moderation in food and



Circadian Rhythms of Autonomic Functions. Figure 2 Model of the metabolic syndrome caused by a central nervous deregulation. The disturbed output of the biological clock effects the selective balance of the autonomic nervous system in different parts of the body. In the intra-abdominal compartment, the ANS is shifted in favor of the parasympathetic branch, resulting in high insulin secretion, growth of intra-abdominal fat tissue and fatty liver. Contrarily, in the thorax and movement compartment the sympathetic branch prevails, leading to high blood pressure and impaired glucose uptake by the muscle. In this model, the symptoms of the metabolic syndrome are the result and not cause of the disease.

carbohydrate intake, results in an increased sympathetic tone to the abdominal compartment and will amplify the daily rhythm in the activity/sleep cycle.

Several studies indicate that the SCN has a major role in diminishing the effect of stressful events. An analysis of the hypothalamus in people/individuals who died of a cardiovascular incident or brain infarct after a long history of hypertension revealed a diminishment of the size of the SCN in hypertensive patients as compared to controls in which the SCN contained at least two times more VP neurons than the hypertensive SCN. Moreover coinciding with the diminished SCN activity, the activity of the CRH neurons in the PVN was increased, indicating that similar as in the rat also in the human brain the biological clock may serve to inhibit the activity of the HPA axis [5]. The main question that needs to be resolved is whether these observed hypothalamic changes are the cause or consequence of hypertension. An indication that a diminishment of SCN activity may occur already before the onset of hypertension is the observation that people who sleep irregular and less than 5 h per night have a three times higher chance to develop hypertension [6]. This fits in our hypothesis that hypertension might be caused by a defective biological clock that is less well able to maintain a longer rest period and to prepare the individual for the upcoming activity period and hence results in cardiovascular problems. Several studies show that in humans especially in the early morning a high incidence of cardiovascular incidents occur. This not only suggests that the organization of the daily transition from the inactivity period to the activity period is sensitive to failure but it may also support our idea that this transition should be prepared by our biological clock. Furthermore, if the biological clock is less active or shows less strong amplitude in its output it might prepare us less well for activity. This may in the long-term lead to disease.

The SCN is not only involved in the organization of the physiology of the body in association with the light–dark cycle but the body also communicates back to the SCN. Hereto, the SCN also receives information from the circulation. The observation that in diseases such as diabetes and hypertension a flattened rhythm is observed in autonomic parameters together with a decrease in activity of the SCN suggests that the biological clock may play an important role in the etiology of these diseases. We can see the interaction of the SCN with the body as a closed circle in which changes in any part of this circuit will result in changes in functions either of the body or the biological clock.

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Circadian Sleep Phase Syndromes

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Synonyms

Circadian rhythm sleep disorders; Circadian desynchronization/circadian desynchrony

Definition

Broadly defined, a ►circadian sleep phase syndrome is when ►sleep occurs at an abnormal or undesirable clock time or occurs out of phase with other endogenous ►circadian rhythms.

Characteristics

Assessing Circadian Disorders with the Dim Light Melatonin Onset (DLMO)

►Circadian rhythm disorders are best characterized by measuring the timing of sleep and the time of the ►dim light melatonin onset (DLMO) in sighted people [or the melatonin onset (MO) in blind people]. In normally phased sighted people entrained to the ►light/dark cycle, ►melatonin is produced by the ►pineal gland only during the hours of nighttime darkness. The plasma $DLMO_{10}$ (10 pg melatonin/ml plasma) occurs on average about 14 h after waketime; therefore, its ►circadian time (CT) is CT 14 [1]. In individuals who are low melatonin producers, a lower threshold is used, 2 pg/ml: the plasma $DLMO_2$ is on average about an hour earlier than the $DLMO_{10}$ and indicates CT 13. Around the time of the ►DLMO, salivary melatonin levels are about one-third those of plasma. Hence, the saliva $DLMO_3$ or $DLMO_{0.7}$ is used to mark CT 14 or CT 13, respectively. Whether at home or in the lab, light exposure should not exceed 10–30 lux after about 5 p.m. (the use of amber-tinted goggles may permit brighter light exposure). The DLMO as defined above almost always occurs before usual sleep onset (when the DLMO is not followed by a subscript, the subscript of 10 for plasma levels or 3 for saliva levels is assumed). Therefore, these collections do not interfere with sleep and can even be done in the sleep lab before polysomnographic studies.

Delayed Sleep Phase Syndrome (DSPS)

The most common circadian phase sleep disorder is ►delayed sleep phase syndrome (DSPS). It is characterized by a tendency to go to sleep late and to wake up late – even after a night of sleep deprivation, it is difficult for these people to go to sleep earlier. The clock time of the DLMO is also delayed in these individuals. DSPS is most common in adolescents. One of the first treatments for it was "chronotherapy [2]," which was based on a theoretical model that postulated two endogenous circadian pacemakers, one that regulates the ►sleep/wake cycle [located in the ►suprachiasmatic nucleus (►SCN) of the hypothalamus] and another that regulates the temperature circadian rhythm (thought by some to be located elsewhere [3]). The scheduling of sleep was thought to have a direct entraining effect on the latter, independent of imposing structure on the light/dark cycle. According to this model, treatment of DSPS consisted of delaying sleep times 3 h per day for 6–7 days, so that the patient would eventually be able to go to sleep earlier.

Beginning with studies in which the sleep/wake cycle was held constant, consensus was eventually achieved on the following points: there is only one ►endogenous circadian pacemaker, it is located in the SCN and it is relatively insensitive to direct phase-resetting effects of sleep compared to those of bright light and melatonin, the two most commonly used phase-shifting agents for treating DSPS, as well as other circadian disorders [4]. Scheduling sleep times remain important, however, particularly because sleep imposes structured darkness upon the perceived light/dark cycle and the latter will have profound phase-resetting effects on the endogenous circadian pacemaker.

Advanced Sleep Phase Syndrome (ASPS)

A less common circadian rhythm sleep disorder is ►advanced sleep phase syndrome (ASPS). However, it is thought to be the most typical phase disturbance of the elderly [5,6]. These individuals awaken early in the morning and have difficulty staying up in the evening. The clock time of the DLMO also is advanced in these individuals. Sleep maintenance insomnia often is related to ASPS.

Treating DSPS and ASPS Based on the Light Melatonin Phase Response Curves (PRCs)

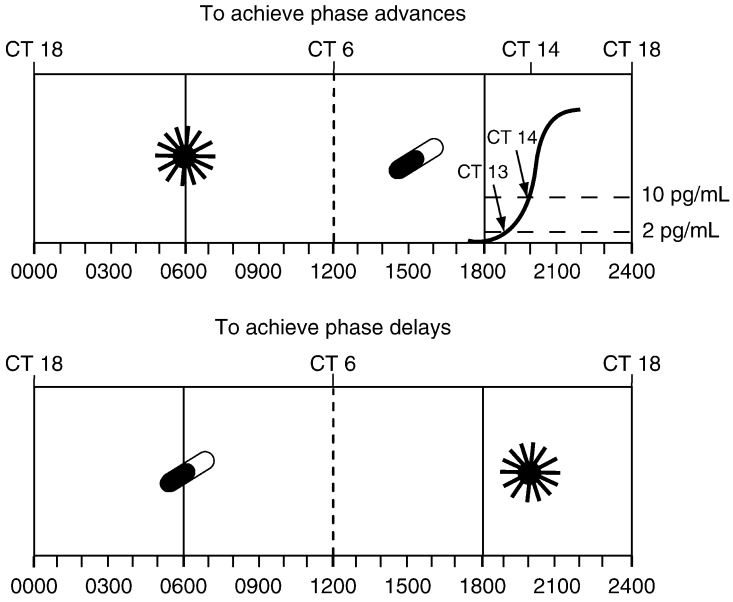
Treatment of these disorders is based on the human ►phase response curves (PRCs) to bright light exposure and low-dose melatonin administration [4]. These PRCs are about 12 h out of phase with each other, because melatonin is a chemical signal for nighttime darkness (Fig. 1). According to the light PRC, bright light exposure causes phase advances when it is scheduled between CT 18 and CT 6 and causes phase delays when it is scheduled between CT 6 and CT 18 (on average, about noon and midnight, respectively, for individuals who usually awaken at 6 a.m.). According to the melatonin PRC, melatonin causes phase delays when it is administered between CT 18 and CT 6 and causes phase advances when it is administered between CT 6 and CT 18.

For treatment of DSPS, bright light (including sunlight) should be scheduled immediately upon awakening. Low-dose (≤0.3–0.5 mg) melatonin should be taken about 8 h later. Because about one in three people experience sleepiness as a side effect of melatonin, particularly at higher doses, an additional 3–10 mg can be taken before bedtime. Waketime and bedtime should be gradually shifted to the desired time. The treatment(s) may need to be continued indefinitely.

For treatment of ASPS, bright light (2,000–10,000 lux) should be scheduled 7 and 9 p.m., ending no later than 1 h before desired sleep time. Melatonin should be taken at each awakening during the night, but only after 1 a.m. The most important melatonin dose is the one taken at final awakening in the morning, which may need to be reduced, so as to minimize soporific side effects that might interfere with early morning activities.

Free-Running Circadian Rhythms

A third type of circadian phase sleep disorder is one in which the individual "free-runs." A ►free-running sleep/wake cycle is very uncommon, however, even



Circadian Sleep Phase Syndromes. Figure 1 The optimal times to schedule bright light exposure and low-dose melatonin administration to cause circadian phase shifts are based on their respective phase response curves (PRCs) which are about 12 h out of phase with each other [4]. The plasma $DLMO_{10}$ (saliva $DLMO_3$), marking circadian time (CT) 14, can be used to indicate when advance and delay responses occur, in order to maximize phase shifts. The crossover times are 8 h before (CT 6), and 4 h after (CT18), the $DLMO_{10}$. Also indicated are clock times typical for individuals who awaken at 6 a.m. (0600). Optimally, exogenous melatonin should overlap with either the onset or the offset of the endogenous melatonin profile. High doses (greater than about 5 mg) may be less effective than lower doses, because of spillover onto the wrong zone of the melatonin PRC. Adapted from Lewy [1], with permission. *DLMO*, dim light melatonin onset.

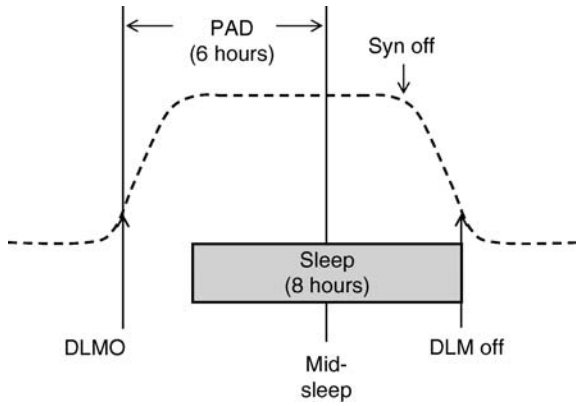
in blind people (in fact, particularly in blind people). A small number of sighted people have free-running disorders, which is often referred to as non-24-h sleep/wake syndrome. It can be treated by daily bright light exposure and low-dose melatonin administration.

Free-running rhythms, best characterized by the circadian rhythm of melatonin production, occur in most totally blind people who have no light perception. Nevertheless, these blind free-runners (BFRs) try to sleep at conventional times. However, when the MO is out of phase with the sleep/wake cycle, sleep quality is poor and daytime sleepiness occurs. The consequential recurrent sleep and mood disorder is a great burden for many BFRs, second only to lack of vision [7]. The pattern of recurrence is related to the ►circadian period (tau). A BFR with a tau of 25 h will go through a complete circadian beat cycle every 24 days: about once a month, sleep quality will be poor for a few days. A BFR with a tau of 24.1 h will go through a complete circadian beat cycle every 240 days: about once every 8 months, sleep quality will be poor for several weeks.

Most BFRs can be treated by taking low-dose melatonin around 6 p.m. A few BFRs should take melatonin at waketime (if they have a tau < 24 h). Also, all BFRs studied to date appear to be more or less sensitive to as-yet-unknown weak ►zeitgebers (that are probably related to social cues) [8]. About 25% of totally blind women and apparently few if any totally blind men are sufficiently sensitive to these zeitgebers so as to be naturally entrained by them. Even bilaterally enucleated BFRs drift faster than average as their MO occurs between about 8 a.m. and 8 p.m. and drift slower than average as the MO occurs between about 8 p.m. and 8 a.m. This pattern appears to be the same in all BFRs. However, some BFRs (usually women) show greater relative coordination to them than other BFRs (usually men). Identification of these weak zeitgebers, which are probably related to social cues, may lead to a third type of treatment modality for circadian rhythm disorders. To a small extent, these weak zeitgebers probably affect the phase angle of ►entrainment of sighted people. Sometimes the weak zeitgebers are referred to as ►non-photic zeitgebers.

The Phase Angle Difference (PAD) Between the DLMO and Mid-Sleep

In ASPS and DSPS, abnormal sleep times have traditionally sufficed for diagnosis and management. However, sleep times alone do not take into account the recent finding that internal circadian misalignment may be an important component in some sleep and psychiatric disorders. First tested in winter depression (►seasonal affective disorder (SAD)), the phase angle difference (PAD) between the DLMO and mid-sleep may be a significant component of this disorder. In healthy, sighted people, PAD = 6 h, on average (Fig. 2). When



Circadian Sleep Phase Syndromes. Figure 2 The phase angle difference (PAD) between the plasma $DLMO_{10}$ (saliva $DLMO_3$) and the time of mid-sleep is on average about 6 h in healthy controls. PAD 6 can be used to phase type individuals and to assess internal circadian misalignment. A person with a PAD > 6 is a phase-advanced type, whereas a person with a PAD ≤ 6 is a phase-delayed type. PAD 6 represents optimal circadian alignment (the "sweet spot" for the DLMO). Deviations from 6 in either direction indicate circadian misalignment, which correlates with increasing depression ratings in seasonal affective disorder (SAD, or winter depression); this finding has helped establish the phase shift hypothesis (PSH) for SAD [9]. Testing the PSH in other psychiatric (and sleep) disorders may also reveal a circadian misalignment component. From Lewy [1], with permission. *SynOff*, melatonin synthesis offset; *DLMOff*, dim light melatonin offset.

PAD = 6, SAD patients are least symptomatic, before and after treatment with a phase-resetting agent. In this study [9], the phase-resetting agent was low-dose melatonin. Appropriately timed melatonin was significantly antidepressant. Future studies of patients with ASPS and DSPS will need to take into account PAD, so as to assure optimal sleep quality. In fact, treating these disorders with too much of a phase-resetting agent can result in causing internal circadian misalignment that might cause depression in vulnerable individuals.

Previously, phase typing was done by assessing sleep times, which could only reliably distinguish between the most extreme cases. The use of PAD 6 offers a way to phase type people who are slightly different from each other. PAD ≤ 6 indicates a DLMO that is delayed with respect to the sleep/wake cycle. PAD > 6 indicates a DLMO that is advanced with respect to the sleep/wake cycle. However, there may be some inter-individual variability. Alternative ways to assess PAD using the DLMO and sleep times are the waketime-to-DLMO interval [DLMO ►zeitgeber time (ZT)] and the DLMO-to-sleep onset interval (melatonin sleep interval, or MSI).

Winter Depression (SAD)

The ►phase shift hypothesis (PSH) for SAD posits that most patients become depressed in the winter at least in part because of the later dawn. This causes a ►phase delay in the circadian rhythms tightly coupled to the endogenous circadian pacemaker (marked by the DLMO) relative to the sleep/wake cycle [9]. A corollary of the PSH is that a smaller subgroup of SAD patients become advance in the winter. The prototypical phase-delayed SAD patient should be treated with bright light exposure in the morning and/or low-dose melatonin in the afternoon/evening, so as to provide a corrective ►phase advance. The atypical phase-advanced SAD patient should be treated with bright light exposure in the evening and/or low-dose melatonin in the morning so as to provide a corrective phase delay.

Although delayed sleep times correspond to a delayed DLMO clock time, they do not necessarily correspond to a delayed PAD – and the same applies to the advance direction. This is because if a DLMO is delayed with respect to mid-sleep, then sleep time will be advanced with respect to the DLMO. Therefore, assessment of circadian rhythm disorders will require knowledge of the person's DLMO and sleep times.

Jet Lag

Phase typing is not necessary in designing treatment strategies for the circadian misalignment component of ►jet lag. This is because a reasonably accurate estimate of DLMO time at destination can be made by adjusting for the number of time zones crossed. Before traveling east, low-dose melatonin should be taken in the afternoon/evening followed by a higher dose at bedtime. Before traveling west, low-dose melatonin should be taken in the morning. The times for low-dose melatonin at destination should then be adjusted according to the direction and number of time zones crossed. For travel across six or fewer time zones, sunlight exposure at destination should occur in the morning after going east and towards the end of the day after going west. For travel across more than six time zones, sunlight exposure should be avoided at these times for the first day or two after arrival, in order to prevent stimulating the "wrong" zone of the light PRC. During these days exposure should occur either in the late morning (going east) or in the afternoon (going west). If these instructions are followed, a phase shift of 3 h per day should occur and the above exposure and administration times should be adjusted accordingly over the course of the next few days.

The Phase Shift Hypothesis (PSH) in Other Disorders

In SAD, circadian misalignment is substantial and necessary, but alone, not a sufficient cause of the disorder. In BFRs, circadian misalignment is necessary and sufficient to be causal. Investigations into the circadian misalignment component of other sleep and psychiatric disorders should lead to increased use of adjunctive phase-resetting agents in appropriately phase-typed individuals. The PSH is expected to be tested in non-seasonal major depression, insomnia and attention deficit hyperactivity disorder (ADHD), among other disorders.

Shift Work Maladaptation and Irregular Sleep Wake Rhythm

Some circadian sleep disorders are schedule-induced. This certainly is the case with ►shift work maladaptation. Few night shift workers reverse their endogenous circadian rhythms, even after a week of sleeping during the day. This is probably due in part to sunlight exposure encountered in the morning on the way home that is stimulating the advance zone of the light PRC, thus preventing the appropriate phase delay to achieve a reversal in circadian phase. Appropriately scheduled bright light and melatonin can be effectively used to do provide the desired phase delay, as well as to provide the desired phase advance for adjusting back to sleeping at night during days off work; however, treatment must be individualized to each person's particular circumstances.

Irregular sleep wake rhythm is characterized by an absence of a clearly defined sleep bout and a clearly defined activity bout whose sum is about 24 h. Sleeping out of phase with the endogenous circadian rhythm of sleep propensity can result in this disorder. However, there are many other possible causes of fragmented sleep.

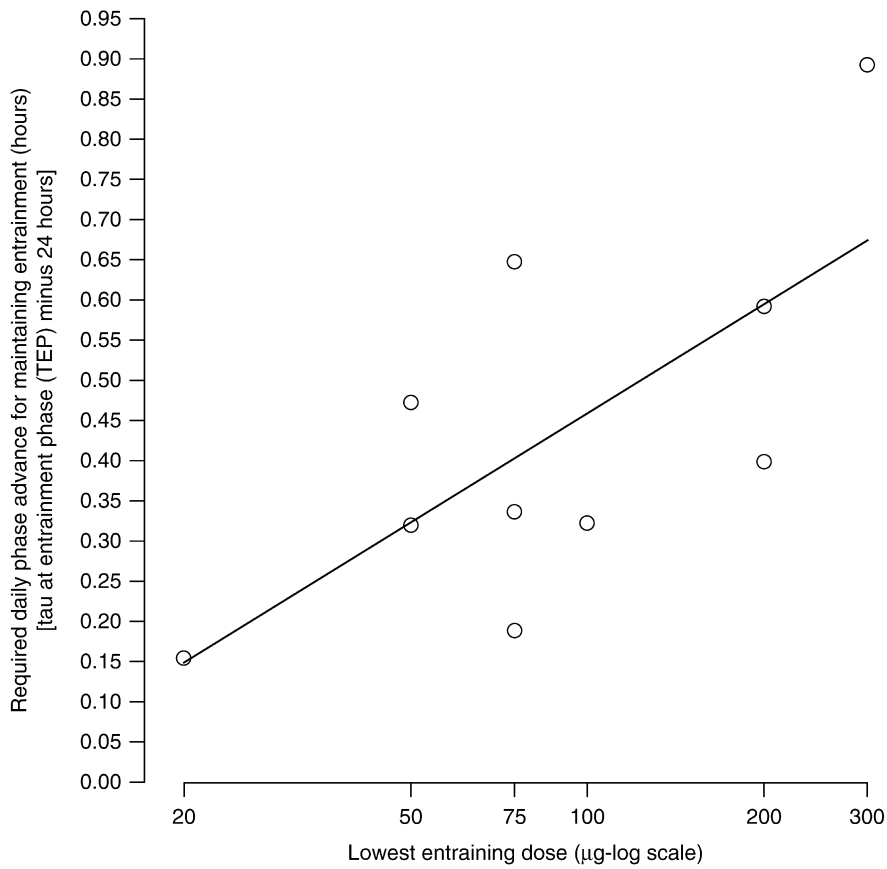
Circadian Phase Typing and Chronotypes

It is important to distinguish between circadian phase typing and chronotypes. The latter is based on questionnaires to identify evening types and morning types. Logically, these chronotypes, also referred to as "night owls" and "morning larks," respectively, might be thought to correspond to phase-delayed types and phase-advanced types. However, preferred sleep times are not always indicative of phase types. Furthermore, as mentioned above, although a DLMO that is delayed with respect to the sleep/wake cycle (i.e., mid-sleep) indicates a phase-delayed type, the sleep/wake cycle in this individual is by definition advanced with respect to the DLMO. While it is technically correct to describe this phase relationship as sleeping at an abnormally early circadian phase, delaying sleep would not necessarily be helpful, because it would delay the perceived light/dark cycle, resulting in a concomitant delay of the DLMO. The treatment of choice for this person would be morning bright light exposure and afternoon/evening low-dose melatonin administration that would provide a corrective phase advance.

Speculating on the Function of Endogenous Melatonin Production

The research done on BFRs during the past few decades can now be applied to sighted perinates. This is because melatonin can entrain BFRs according to a physiological dose-response curve [10]. This curve was constructed by determining the lowest entraining dose for each of ten BFRs. Depending on their tau (actually, tau at entrainment phase, or TEP), the amount of phase advance per day could be calculated necessary for entrainment. When TEP – 24 h is plotted on the ordinate and the lowest entraining dose is plotted on the abscissa, the log-linear regression line is statistically significant (Fig. 3). BFRs can be entrained to very low doses of melatonin (10 μg [1]), three orders of magnitude less than those used formerly (10 mg [7]). Efficacy of low, physiological exogenous doses suggests that endogenous melatonin production may have a circadian function. This function may be to augment entrainment to the light/dark cycle.

However, this function may be redundant, except for sighted perinates. Another future application of this work may be in perinates, to help them sleep at night (when their mothers prefer to sleep). Although vision is possible shortly after birth, entrainment to the light/dark cycle occurs a few months later. Before this time, the infant may require another signal in order to maintain entrainment to the 24-h day of their parents. Entrainment to the mother's sleep/wake cycle may help the mother sleep better and deliver better maternal care, even if it makes no other difference to the perinate. This means that the amount of melatonin in breast milk may be sufficient to entrain the suckling infant, provided the mother is not exposed to too much bright light



Circadian Sleep Phase Syndromes. Figure 3 Physiological dose-response curve for melatonin in humans. The lowest dose found to entrain each of ten blind free-runners (BFRs) is plotted on the abscissa. The daily phase advance required for entrainment is plotted on the ordinate and is calculated for each BFR by subtracting 24 h from tau at entrainment phase (TEP). TEP is the BFR's tau when the MO (melatonin onset) was previously free-running across the clock time at which it has now been entrained to a daily dose of melatonin taken in the early evening (see text and Emens et al. [8]). Doses even lower than 20 μg are effective if tau is close to 24 h [1], which suggest that endogenous melatonin production may have a circadian function in humans. The regression line ($r = 0.69$) is statistically significant ($p = 0.026$). From Lewy et al. [10], with permission.

during the night. During the third trimester, melatonin produced by the mother crosses the placenta and is available to stimulate ►melatonin receptors in the SCN.

Conclusion

In conclusion, circadian phase sleep disorders are best assessed using sleep times and the DLMO. These occur late in phase-delayed types and early in phase-advanced types. In a sense, they are redundant, obvious and exoteric. More esoteric, but no less important, is the time interval between the DLMO and mid-sleep: this PAD represents the degree of internal circadian misalignment, which is important in SAD and may be an important component in other circadian phase sleep and psychiatric disorders. As basic investigations progress in this area of neuroscience, it is expected that the salivary DLMO and PAD will move beyond being just research tools and will become standard clinical tests as well. The PSH for SAD is expected to undergo further testing in other patient populations.

There are at least three ways in which the DLMO is useful. One, it is the basis for phase typing, particularly in combination with sleep times and its timing relative to the sleep/wake cycle (PAD). Two, it indicates the phase of the light and melatonin PRCs, so that treatment using these phase-resetting agents can be optimized. Three, it provides a way of monitoring the induced phase shift.

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Circadian Time

Definition

A standard marker of time that is based upon the free-running period of an oscillation or rhythm. By convention, circadian time 0 (CT 0) is defined as the initiation of activity in a diurnal organism. Likewise, CT 12 is defined as the initiation of activity in a nocturnal organism.

►Circadian Cycle
►Clock
►Human Circadian Timing System

Circannual Rhythms

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Definition

Endogenously generated biological rhythm with a period length approximating to 1 year.

Characteristics

The term circannual rhythm is a derivative of the term circadian. ►Circadian rhythms are endogenously generated biological rhythms with a period length of approximately one day (from the Latin *circa diem*). Correspondingly then, a circannual rhythm may be defined as annual. There are many different examples of circannual rhythms including the pupation rhythm in carpet beetles [1], the urge to migrate in birds [2], hibernation cycles in ground squirrels [3], and cycles of reproductive activity and moulting in ungulates [4].

In species living outside of the equatorial zones, the seasonal change in the daily pattern of light/dark exposure, (that is, the ►photoperiod), is the major synchronising signal for circannual rhythms. Responsiveness to photoperiodic changes ensures that appropriate physiological or behavioral responses occur at the different phases of the sidereal year. Thus, to explore the endogenous component of circannual rhythms, it is necessary to hold organisms on constant photoperiods for long durations (years), this being analogous to holding animals on constant light or constant darkness to explore circadian rhythms. Consequently, research into circannual rhythms is very long-range, which has no doubt been partly responsible for the relatively low level of research activity on this subject.

It is interesting to consider the possible selective benefit that maintaining an endogenous long term timing mechanism might confer. For animals living above ground, such benefit may be very subtle, being limited to those phases of the year during which changes in the environmental photoperiod occur slowly, near to the summer and winter solstices. Here, it may be envisaged that the endogenous "circannual" component allows animals to initiate preparative changes in physiology in readiness for the forthcoming autumn/spring. This anticipation argument has been widely used also to account for circadian ►rhythmicity, but direct experimental evidence for or against this adaptive conjecture is lacking.

The preparative argument is probably strongest for those animals undergoing torpor or ►hibernation during the winter season, as a consequence of which they do not monitor the prevailing photoperiod for several months. In many species, this does not prevent precise timing of the end of the hibernation phase, such that individuals emerge each year in a remarkably consistent time-window. Strong ecological arguments based upon resource availability or competition can be made to support the benefit of achieving such tight long term timing of emergence.

A comparison of the basic features of circannual rhythms, suggests that generally have a period length of less than 1 year – approximately 40 weeks in most instances [1–4]. There have been limited efforts to examine the phase-dependent ►resetting of circannual rhythms by changes in day length, but published work argues for "►Type 0" resetting of the circannual rhythm in beetles and sheep [1,4]. Here, the new phase is independent of the phase at which the resetting stimulus is applied (giving a slope of 0 when new phase is plotted against old phase). In the circadian context, this type of resetting response has been suggested to be indicative of a weak underlying ►oscillator [5], and this may be linked to the fact that circannual rhythms often show considerable instability and dampening under constant photoperiodic conditions.

Compared to circadian rhythms, much less is known about the underlying physiological mechanisms driving circannual rhythms, and their relationships to the machinery governing photoperiodic response mechanisms. In terms of formal mechanism, three distinct possibilities can be envisaged: (i) circannual rhythms are an emergent property of circadian rhythms, through a process known as frequency demultiplication; (ii) they emerge as consequence of transitions through a sequence of stages each of fixed duration; and (iii) a true circannual oscillator exists analogous to a circadian oscillator. Of these, the first is not favoured since experiments in which animals are entrained to daily photoperiod cycles with periods unequal to 24 h do not lead to proportionate changes in circannual rhythm duration. It is very difficult to distinguish between the latter two possibilities partly because data on the neuroanatomical basis of circannual rhythm generation are absent.

Recent studies in the Soay sheep may lead to progress on this front. In common with other seasonal mammals, the photoperiodic response mechanism in this animal can be traced to the pineal neurohormone ►melatonin, and its target sites within the neuroendocrine system. Recent work suggests that circannual rhythm of prolactin secretion in Soay sheep depends on processes within one melatonin target tissue, the *pars tuberalis* region of the anterior pituitary, and that a maintained nightly pattern of melatonin exposure is crucial for expression of the circannual prolactin rhythm [6]. It remains unclear whether this anatomical implication of the *pars tuberalis* in circannual rhythm expression reflects is role as a circannual ►pacemaker, or as part of a network of tissues serving this function.

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Circumvallate Papillae

Definition

(Papilla: small protuberance, Circum: around, Vallum: rampart). These structures are distributed along a chevron shaped line on the dorsal-posterior surface of the human tongue in front of the sulcus terminalis. Each circumvallate papilla has the appearance of a dome surrounded by a horseshoe-shaped invagination opening a trench under the surface of the tongue. The walls of the trench are covered with up to 800 taste buds opening into it and the base of the moat is irrigated by the ducts of the von Ebner gland. Their total number varies between 3 and 13 per individual. They all contain taste buds.

►Taste

Circumventricular Organ

Definition

A small, highly vascular neural region within the brain that protrudes into the third or fourth ventricle and lacks a functional blood-brain barrier (BBB). By this strict Definition, the organum vasculosum of the lamina terminalis, subfornical organ, median eminence, and area postrema are all circumventricular organs. Classically, however, some authors have included other sites, such as the subcommissural organ (which does not lack a BBB), choroid plexus (does not contain any neural elements), posterior lobe of the pituitary gland (located outside the brain), and pineal gland (located outside the brain). The neurons and glia within most circumventricular organs monitor the concentrations of ions and hormones in the blood plasma, and adjust various autonomic and behavioral functions via axonal connections to nuclei in the hypothalamus, brainstem, and other subcortical regions. Other sites, particularly the median eminence, represent a site of axonal transmission of transmitter molecules directly into a portal capillary network.

Cis-regulatory Element

Definition

A discrete region of DNA that affects transcription of a gene.

c-Jun

Definition

A member of the Jun family of proteins that form a component of the AP-1 transcription factor. c-Jun dimerizes with other molecules including other Jun or Fos family members to form transcriptionally active complexes. The expression of c-Jun and the activation of the AP-1 transcription factor complex are increased in response to neurotrophic molecules as well as axonal injury.

►Neurotrophic Factors in Nerve Regeneration

c-Jun N-terminal Kinases (JNKs)

Definition

The c-Jun N-terminal kinases (JNKs) comprise one of the subfamilies of the mitogen-activated protein kinases (MAPK). JNK-mediated phosphorylation activates c-Jun, a component of the AP-1 transcription factor, in response to neurotrophin signaling. JNK activation regulates AP-1-dependent target genes involved in cell proliferation, cell death, inflammation, and DNA repair.

Cladistic Relationships

Definition

Those relationships between species that are based on evolutionary history.

►Evolution of the Brain: in Birds

Cladogram

Definition

Branching diagram of taxa exclusively based on shared derived characters (synapomorphies).

►Evolution of the Brain: In Fishes
►Evolution of the Cerebellum
►Evolution of the Telencephalon: In Anamniotes

Clasp-knife Reflex

Definition

Sudden yield to passive slow stretch of muscles with increased resistance in spastic patients, this yield depending on muscle length and joint angle; differential sign to distinguish increased muscle resistance in ►spasticity from ►rigidity as appearing, e.g., in ►Parkinson disease.

►Parkinson Disease
►Spasticity

Classical Architecture

Definition

A cognitive system has a classical architecture if its cognitive processes rely on structure-sensitive manipulations of symbols.

►Representation (Mental)

Classical Conditioning (Pavlovian Conditioning)

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Synonyms

Responding Conditioning

Definition

A type of associative learning between the successively applied two stimuli resulting in prediction of the second stimulus by the first stimulus.

Classical conditioning, which was formalized by Pavlov in 1906, is a type of associative learning in which the neutral ►conditioned stimulus (CS) comes to evoke a ►conditioned response (CR) that is similar to the ►unconditioned response (UR) induced by the ►unconditioned stimulus (US) after repetitive pairings of the CS with the US. In order to elucidate the brain mechanisms of such an associative learning, ►conditioned taste aversion (CTA) that is defined as a learned association of taste (CS) with malaise (US) is extensively studied because CTA is firmly acquired by single association of the CS and the US even with a long CS–US interval.

Characteristics

Basic Nature of Classical Conditioning

There are two forms of conditioning: one is classical conditioning and the other is operant conditioning. Classical conditioning is also referred to as respondent conditioning or Pavlovian conditioning. Apart from operant conditioning, the subject learns relations between stimuli, i.e., classical conditioning is a type of associative learning formed by pairing of unconditioned stimulus (US) with the conditioned stimulus (CS). In the case of salivation conditioning experiments in dogs by Pavlov [1], repetitive pairings of a neutral stimulus such as a metronome sound with the following exposure to a small amount of meat powder were conducted. Salivary secretion was evoked by the meat powder presentation, but not by the metronome sound per se at the beginning of pairings; salivary secretion, however, was gradually evoked by the metronome sound with the repetition of pairings. The neutral metronome sound to which conditioning was acquired is the CS, and the salivation induced by the CS is referred to as the conditioned response (CR). The meat powder is the US and the innate reflex salivary secretion to the US is the unconditioned response (UR). In classical conditioning, the USs are chosen so that they elicit reflex responses as URs, such as salivary secretion, changes of skin resistance, vasomotor responses, and visceral responses, as the autonomic reactions, and flexion reflex, patellar tendon reflex, and eyelid reflex as the muscle movements.

For the successful establishment of conditioning, the timing and the order of the presentation of the CS and US are important. The CS should be presented before the US onset and should terminate during the US presentation or at the US onset. When the onset time of the CS coincides with that of the US, conditioning is effective provided that the CS terminates before the US. If the CS starts and ends before the US starts (or the CS and US are not overlapping) and the interstimulus interval (the time period between the end of the CS and the start of the US) is short (usually within the second range), conditioning is attained. If the US onset precedes the CS onset and the US terminates before the CS, this protocol (backward conditioning) is usually ineffective.

The strength of the acquired conditioning can be influenced depending on the properties and relationships of the CS and US. The followings are examples:

1. *Conditioned Inhibition*. A CS– that is conditioned to the absence of the US inhibits the development of the CR to a mixed stimulus of CS– and CS+ compared with the CR to the CS+ that is solely conditioned to the presence of the US [1].

Classical Conditioning (Pavlovian Conditioning). Table 1 Characteristics of classical conditioning (CC) and taste aversion conditioning (TAC)

	CC	TAC
Association learning between CS and US	o	o
CS should precede US	o	o
CS should be novel	o	o
CR is generalized to similar CSs	o	o
CR can be extinguished	o	o
Necessary pairing of CS and US	Repetitive	One
Interval between CS and US	Short (within seconds)	Long (up to several hours)

CS, conditioned stimulus; US, unconditioned stimulus; CR, conditioned response; o, yes.

2. *Latent Inhibition*. A CS that has been repeatedly presented in the absence of the US requires more pairings with the US to elicit the CR [2]. Such lowered conditioning performance, called latent inhibition, may be derived from the diminution of novelty of the CS and the development of safe learning leading to a failure to new association to such stimuli or a failure of retrieval even if the association of the preexposed CS to the US proceeds normally.
3. *Overshadowing*. When two CSs with markedly different salience (CS+ vs. CS+++) are presented as a compound CS, CS+ forms a much weaker CR than it would in the presence of only the CS+, whereas the CR to the CS+++ remains undiminished [3]. The stronger CS may overshadow the weaker CS.
4. *Blocking*. A well-established CS presented on later conditioning trials in compound with a new stimulus blocks the new stimulus from associating with the US [4].
5. *Second-Order Conditioning*. Animals presented with a novel CS followed by presentation of the well-established CS without presentation of the US acquire the CR to the novel CS [5].

Psychologists have introduced a number of sophisticated theories of associations [6]. However, There is no accepted unified theory covering all manifestations and properties of classical conditioning [7].

Conditioned Taste Aversion

CTA, or taste aversion conditioning is widely accepted as a kind of Pavlovian learning in which animals acquire an aversion to a tastant (CS) that has been associated with visceral distress or malaise (US) [8]. Following a CTA, reexposure to the CS elicits aversive behaviors that are similar to those shown to innately aversive tastants such as quinine. When saccharin is used as the CS and an intraperitoneal injection of 0.15 M LiCl (2% of body weight) as the malaise-inducing CS, the sweet and palatable taste is treated as an aversive taste after CTA acquisition. The quality itself may not change, whereas the perceived intensity may be enhanced to facilitate detection of the harmful substance, and a hedonic shift from positive to negative occurs. As shown in Table 1, besides the similarities to classical conditioning, CTA has the following characteristics that are distinguished from classical conditioning: (i) Strong CTAs to novel taste stimuli can be established in a single learning procedure, i.e. after one pairing of CS and US. (ii) Successful CTAs can develop to the CS after delays of as long as 4–12 h between exposure to the CS and delivery of the US. (iii) The association between the CS and the US can proceed under deep pentobarbital anesthesia. (iv) The aversive behavior to the CS is not the CR because an intraperitoneal injection of LiCl does not elicit aversive taste reactivity as the UR. One of the URs induced by LiCl injection is lowered temperature, and it is shown that after acquisition of CTA, gustatory stimulation with the CS elicits lowered body temperature, indicating that CTA is really a Pavlovian conditioning. Consequently, CTA has two aspects: one is classical conditioning and the other is fear conditioning (or fear learning where a stimulus becomes associated with fear).

The single learning procedure with the long CS–US interval enables CTA to be a good model to elucidate the neural substrate, neuroactive substances involved and cellular and molecular processes [9,10] in the relevant areas of the brain concerning the acquisition, consolidation, and retention of the associative learning.

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Classical Mechanics

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Definition

The term classical mechanics refers to the study of the motion of particles, systems of particles and rigid bodies as understood before the advent of relativity and quantum mechanics, that is, roughly until the dawn of the twentieth century. It is important to bear in mind that the new physics inaugurated by these two disciplines did not invalidate the results of classical mechanics, a discipline that still remains at the foundation of most of engineering and biomechanics. Classical mechanics can be divided into two major sub-disciplines, ►Newtonian mechanics and ►analytical mechanics.

Description of Theory

The basic geometric idea of ►analytical mechanics is that of ►*configuration space* of a mechanical system. If the system is considered as a whole, rather than as an assembly of interconnected material points, the configuration space is a geometrical representation of all the possible configurations that the system can attain. Mathematically speaking, the configuration space is assumed to be a ►differentiable manifold. As a non-trivial example of the conceptual difference between the ►Newtonian mechanics approach and that of ►analytical mechanics, consider a plane double pendulum, namely, a material particle linked by a massless rigid bar to a fixed point of suspension and to another material particle by means of a similar link. (This example is kinematically similar to the two-bone system discussed in the article ►Statics. The particles are assumed to move in a vertical plane. From the point of view of ►Newtonian mechanics, to obtain the equations of motion of the system each of the two particles would have to be isolated and its equations of motion written, taking into account the fact that the rigid links provide unknown reactive forces (each acting, in this case, in the direction of one of the bars). Taking advantage of the extra information provided by the geometric constraints (in this case, the constant distance between the first particle and the point of suspension, and the constant distance between the two particles), two extra (algebraic) equations can be obtained which, when coupled with the equations of motion, allow for the solution of the motion and of the forces of constraint. This method has at least two drawbacks. The first is that for systems with multiple geometric constraints the formulation can become very cumbersome. The second drawback is that the resulting system of equations is a mixture of algebraic and differential equations, with the ensuing numerical problems. Although it may be said that with today's computing power these are not major drawbacks, there are deeper physical and mathematical reasons to look at the system in a global manner that may be able to factor out the geometrical constraints. In the case of the double pendulum, it is just necessary to observe that the first particle can only move in a circle around the fixed point, while the second particle can only occupy positions that lie on a circle around the instantaneous position of the first particle. A moment's reflection reveals that the collection of all possible configurations of the system describes, therefore, the surface of a torus (a doughnut), which becomes the configuration space of the system in this particular case. The configuration space does not carry any special system of coordinates, but such a system can be chosen (at least locally). For example, the angular deviations of the links from the vertical direction, or the horizontal distances from the vertical line through the point of suspension, will do as *generalized coordinates*. At any rate, the number of coordinates (the *dimension* of the configuration space) in the example is just two. In general, the dimension of the configuration space is equal to the number of true degrees of freedom the system possesses. Unlike in Newtonian mechanics, the geometrical constraints are already incorporated in the definition of the space itself and, as a result, the forces of constraint may be eliminated altogether from the analysis.

A useful way to understand the transition from classical to analytical mechanics is provided by the ►principle of virtual work.

Newtonian Mechanics

At the outset, classical mechanics postulates the existence of *material points* or *particles* endowed with an invariant strictly positive scalar property called *mass*. Another primitive concept of classical mechanics is *classical space-time*. The precise definition of this entity is beyond the scope of this article, but an intuitive way to visualize it is to imagine that to each point of a real line (the time line) is attached a Euclidean space (a space of points where the theorem of Pythagoras is valid globally). An *event* is a point in space-time. Given two events, it can be established whether or not they correspond to the same time (*absolute simultaneity*). Given two non-simultaneous events, on the other hand, it is impossible to determine in an absolute way whether or not they correspond to the same location. Thus, in classical mechanics, time is absolute, but space is not. Only for simultaneous events can their relative locations be unequivocally ascertained. The gap is filled by the notion of (classical) *observer*. An observer (or frame) is defined by choosing smoothly, for every instant of time, an origin (an event) and three mutually perpendicular directions. Thus, any event can be assigned a *position vector* $\mathbf{x}$ relative to a given observer. A *motion* of a particle is a smooth assignment of an event to each instant of time. For an observer, therefore, the motion of a particle consists of a time-dependent position vector $\mathbf{x}(t)$. The same motion, as seen by a different observer, will be denoted by, say, $\mathbf{x}^*(t)$. For simplicity, it is assumed that both observers have synchronized their clocks. The relation between $\mathbf{x}^*(t)$ and $\mathbf{x}(t)$ cannot be completely arbitrary, since both observers must agree on the measurement of distances between simultaneous events. As discussed under ►kinematics of deformation, the most general relation between the position vectors is:

$$\mathbf{x}^*(t) = \mathbf{c}(t) + \mathbf{Q}(t)\,\mathbf{x}(t), \tag{1}$$

where $\mathbf{c}(t)$ is a time-dependent vector and $\mathbf{Q}(t)$ is a time dependent rotation (represented in a coordinate system by a proper orthogonal matrix). The ►*velocity* $\mathbf{v}(t)$ and ►*acceleration* $\mathbf{a}(t)$ of a particle relative to an observer are, respectively, given by the first and second time-derivatives of the position vector, namely: $\mathbf{v}(t) = \dot{\mathbf{x}}(t)$ and $\mathbf{a}(t) = \ddot{\mathbf{x}}(t)$. By differentiating (1), the following relations between the observed velocities and accelerations of the same motion as seen by two observers are obtained:

$$\mathbf{v}^*(t) = \dot{\mathbf{c}}(t) + \dot{\mathbf{Q}}(t)\,\mathbf{x}(t) + \mathbf{Q}(t)\,\mathbf{v}(t), \tag{2}$$

$$\mathbf{a}^*(\mathbf{t}) = \ddot{\mathbf{c}}(t) + \ddot{\mathbf{Q}}(t)\,\mathbf{x}(t) + 2\,\dot{\mathbf{Q}}(t)\,\mathbf{v}(t) + \mathbf{Q}(t)\,\mathbf{a}(t). \tag{3}$$

Two observers are *inertially related* if $\ddot{\mathbf{c}}(t) = \dot{\mathbf{Q}}(t) \equiv 0$ (they recede at a constant velocity without rotating). Thus, all observers can be partitioned into equivalence classes of inertiality. It follows from (3) that all inertially related observers agree on the value of the acceleration vector of a particle (although they in general disagree on the position and velocity vectors). By "agreement" it is meant that their measurements differ only by the (constant) rotational correction, but are not otherwise affected by the relative state of motion of the observers. Newton's *first law of motion* postulates that among all these inertial classes there exists a privileged one for which the laws of mechanics appear particularly simple. A frame belonging to the privileged class is called an *inertial frame*. To recognize an inertial frame, it is necessary to accept another primitive concept, that of *force*. In the absence of forces, Newton's first law asserts that the motion of a particle as seen from an inertial frame has a constant velocity (equivalently, zero acceleration). Thus, forces are not the causes of motion, but rather the causes of change of motion relative to an inertial frame. Newton's *second law of motion* quantifies this idea by asserting that the force $\mathbf{f}$ impressed upon a particle is directly proportional to its acceleration in an inertial frame, and that the constant of proportionality is the mass of the particle. This is the famous equation:

$$\mathbf{f} = m\mathbf{a}. \tag{4}$$

An equivalent way to state this law, more in the spirit of Newton's original verbal formulation, can be obtained by defining the *momentum* of a particle (relative to an observer) as the vector $\mathbf{p} = m\mathbf{v}$, where m is the mass of the particle. In terms of the momentum, (4) reads:

$$\mathbf{f} = \dot{\mathbf{p}}, \tag{5}$$

thus evidencing the cause-effect relationship between forces and changes of momentum. To solve a particular problem in Newtonian particle mechanics, all that needs to be known is the force applied as a function of time and/or position and/or velocity, and the *initial conditions*, namely, the position and velocity for a specific (initial) time. The theory of ordinary differential equations then ensures the existence of a solution of (4), at least for some interval of time.

Consider now a *system of N particles* of masses m_i ($i = 1,...,N$). It is now possible to distinguish between forces exerted upon each particle by the external world and forces exerted by the particles upon each other. The first kind may be called *external forces* and the second kind *internal forces*. (Naturally, the choice of the "system" is in the hands of the analyst. For example, considering a subsystem with less particles, say $N' < N$, the effect of the remaining N-N' particles on this subsystem must now be considered as part of the external forces). Let $\mathbf{f}_i^{ext}$ denote the external force acting on the i-th particle and let $\mathbf{f}_{ij}$ represent the (internal) force exerted by particle j upon particle i. Newton's

third law assumes that the internal forces abide by the *principle of action and reaction*. According to this principle, $\mathbf{f}_{ji} = -\mathbf{f}_{ij}$. In words the force exerted by particle i on particle j is a vector belonging to the line joining both particles and is equal in magnitude, but opposite in sense, to the force exerted by particle j on particle i. An immediate consequence of this principle is that a particle does not exert a force on itself (i.e. $\mathbf{f}_{ii} = \mathbf{0}$). This principle does not stand on the same footing as the first two laws, since the possibility of forces not abiding by it is not excluded. It is more than anything else a statement of the assumptions made to obtain specific results that are applicable in many cases of interest (Newton, of course, had in mind mainly the forces of gravitational attraction). Be that as it may, the total force acting on particle i is $\mathbf{f}_i^{total} = \mathbf{f}_i^{ext} + \sum_{j=1}^{N} \mathbf{f}_{ij} = \dot{p}_i$, using (5). Adding these expressions over i, it can easily be seen that the internal forces cancel out, and we obtain the important equation:

$$\mathbf{F}^{ext} = \dot{\mathbf{P}}, \tag{6}$$

where the $\mathbf{F}^{ext} = \sum_{i=1}^{N} \mathbf{f}_i^{ext}$ is *the total external force*, and $\mathbf{P} = \sum_{i=1}^{N} \mathbf{p}_i$ is the *total momentum* of the system. Defining the *center of mass* of the system as the point whose position vector is given by the average: $\bar{\mathbf{x}} = \frac{1}{M} \sum_{i=1}^{N} m_i \mathbf{x}_i$, where $M = \sum_{i=1}^{N} m_i$ is the total mass, it is easy to show that the total momentum is equal to the momentum of a fictitious particle of mass M moving with the center of mass of the system. The *theorem of the center of mass* is thus produced: the center of mass of a system of particles interacting according to Newton's third law moves as if it were a particle whose mass is the total mass of the system subjected to the vector sum of all the *external* forces acting on the system.

The ▶*angular momentum* of the particles is next considered. By definition, the angular momentum with respect to a point O (which, for convenience, is identified with the origin of the inertial frame) is equal to the cross product $\mathbf{h}_i^O = \mathbf{x}_i \times \mathbf{p}_i$. A reasoning similar to the one just exposed leads to the following result:

$$\mathbf{M}_O^{ext} = \dot{\mathbf{H}}_O, \tag{7}$$

where $\mathbf{M}_O^{ext} = \sum_{i=1}^{N} \mathbf{x}_i \times \mathbf{f}_i^{ext}$ is the total moment of the external forces and where $\mathbf{H}_O = \sum_{i=1}^{N} \mathbf{h}_i^O$ is the total angular momentum of the system. Equations (6) and (7) are both indicative of average quantities of the motion of the system; much in the same way as the mean and the standard deviation of a statistical distribution give a good indication of the nature of the distribution. But, just as in the statistical analogy, these two quantities are not sufficient to completely characterize the distribution, so too in the case of a system of particles the knowledge of the total momentum and total angular momentum is not sufficient to determine the detailed motion of each particle of the system. There is, however, one instance for which these quantities *are* sufficient; this is the case of a *rigid system*. (Without pursuing the analogy any further, this case is the counterpart of the normal Gaussian distribution).

A (discrete or continuous) system of particles is said to be *rigid* if the distances between particles are pairwise constant in time. Under these conditions, it can be shown that the most general motion of a rigid system can be described by the motion of any one of its points (the center of mass, say) and a time-dependent rotation. In other words, although the physical meaning is different, the most general form of a *rigid-body motion* is given by (1), which can be rewritten as:

$$\mathbf{x}(t) = \bar{\mathbf{x}}(t) + \mathbf{R}(t)\,\mathbf{x}', \tag{8}$$

and interpreted as follows. Let primes denote quantities measured in a frame whose origin is at the center of mass and which is "frozen" within the system (in other words, the three perpendicular axes defining the frame are made up of material particles). Thus, $\mathbf{x}'$ denotes the position vector of a particle relative to this *material frame*. It is precisely for this reason that the dependence on time has been dropped; in a material frame (moving as it does in unison with the rigid body) the particles appear not to move at all. The orthogonal operator $\mathbf{R}(t)$ and the vector $\mathbf{x}(t)$represent the rotational and translational components of the change of frame, from an inertial frame of reference to the material frame. It follows from (2) and (3) that the velocity and acceleration vectors, with respect to the outer inertial frame, of an arbitrary particle of the rigid system are given respectively by:

$$\mathbf{v}(t) = \dot{\bar{\mathbf{x}}}(t) + \dot{\mathbf{R}}(t)\,\mathbf{x}', \tag{9}$$

$$\mathbf{a}(t) = \ddot{\bar{\mathbf{x}}}(t) + \ddot{\mathbf{R}}(t)\,\mathbf{x}'. \tag{10}$$

The nine entries of an orthogonal matrix can at most depend on three independent parameters, since they have to abide by the six constraints of orthonormality. It can be concluded that the most general motion of a rigid body is completely describable by means of six quantities (or *degrees of freedom*), namely, the three coordinates of its center of mass and the three independent parameters of the rotation matrix. Equations (6) and (7) constitute a system of six ordinary differential equations and it turns out that they are

independent and that their solution allows in principle (with appropriate initial conditions) the obtaining of the time evolution of the six degrees of freedom just described. This is the content of *Euler's theorem*, which, by a judicious choice of variables, provides a more explicit form of the equations of motion. To sketch this important result, the total angular momentum of a rigid system (assumed to be discrete and finite, for simplicity) is evaluated. By definition:

$$\mathbf{H}_0 = \sum_{i=1}^{N} \mathbf{x}_i \times \mathbf{p}_i = \sum m_i(\bar{\mathbf{x}} + \mathbf{R}\,\mathbf{x}_i') \times (\dot{\bar{\mathbf{x}}} + \dot{\mathbf{R}}\,\mathbf{x}_i') = \bar{\mathbf{x}} \times \mathbf{P} + \mathbf{J}\omega, \quad (11)$$

where use is made of (8) and (9) and the fact that $\bar{\mathbf{x}}$ is the position of the center of mass. The symbol $\mathbf{J}$ stands for the symmetric positive-definite *tensor of inertia*, which can be calculated in the inertial frame as:

$$\mathbf{J} = \sum_{i=1}^{N} m_i \left(trace\,(\mathbf{R}\mathbf{x}_i \otimes \mathbf{R}\mathbf{x}_i)\mathbf{I} - (\mathbf{R}\mathbf{x}_i \otimes \mathbf{R}\mathbf{x}_i)\right), \quad (12)$$

where $\mathbf{I}$ is the identity tensor and $\otimes$stands for the tensor product. The vector ω appearing in (11) is the *angular velocity vector*. It is defined as the vector equivalent (through the cross product) to the skew-symmetric tensor $\Omega = -\dot{\mathbf{R}}\mathbf{R}^T$. The tensor of inertia $\mathbf{J}_M$ in a material frame is independent of time and can be calculated once and for all (using $\mathbf{x}_i$ instead of $\mathbf{R}\mathbf{x}_i$ in (12)), with the result that:

$$\mathbf{J} = \mathbf{R}\mathbf{J}_M\mathbf{R}^T. \quad (13)$$

To obtain ►Euler's equations, the *principal axes of inertia* are chosen as a material frame (so that $\mathbf{J}_M$ attains a diagonal form), the time-derivative of (11) is taken and finally the result is transferred back to the moving material frame. From the practical point of view, this classical reduced form of the equations of motion is hardly necessary. It should be clear from (11) and (12) that (6) and (7) provide a system of six ordinary differential equations for the six degrees of freedom of a rigid body.

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C

Classical Neurotransmitters

Definition

The classical neurotransmitters are a collection of small molecular weight molecules that meet specific criteria for chemical neurotransmission. They are generally divided into three main classes: cholinergic, biogenic amine or monoamines, and amino acid transmitters.

►Acetylcholine
►Monoamines

Clathrin-mediated Endocytosis (CME)

Definition

Is a prominent cellular mechanism by which membrane proteins internalize from the plasma membrane via the formation of clathrin coated endocytic vesicles. The process involves three distinct steps. In step 1 an adaptor protein recognizes and recruits a membrane protein into a segment of the plasma membrane that will become the endocytic vesicle. A common adaptor of CME is the tetromeric adaptor protein complex-2 (AP-2). The interaction is mediated via a sequence specific motif within the intracellular domain of the membrane proteins and a subunit of the AP-2 complex. In addition to a direct interaction with AP-2, AP-2 accessory proteins can also be involved in the recognition of membrane protein, such as the recruitment of mono-ubiquitinated membrane proteins by the AP-2 accessory protein the epidermal growth factor substrate 15 (EPS15). In step 2 (which probably occurs coincident with step 1) the AP-2 complex recruits clathrin and certain accessory proteins, such as the neuron-specific AP180 or its ubiquitously expressed homolog the

clathrin assembly lymphoid myeloid leukemia protein (CALM), to this membrane segment. These accessory proteins promote the localized polymerization of clathrin into a polyhedral lattice. AP-2 as well as several of these accessory proteins encode binding sites for phosphatidylinositol (4,5)-bisphosphate (PIP2), a prominent lipid found in the plasma membrane and this helps to anchor and localize coat formation at the plasma membrane. Other accessory proteins such as Epsin encode a highly conserved Epsin N-terminal homology (ENTH) domain, that can induce membrane curvature via insertion of an α-helix into the outer leaflet of the membrane. This function promotes the membrane invagination of the forming coated pit, while the clathrin lattice stabilizes the curvature. AP-2 therefore plays a central role in clustering and linking the membrane protein to a complex of proteins that promotes formation of the growing clathrin coated pit (CCP) and the subsequent clathrin-coated vesicle (CCV). In step 3 the membrane connecting the CCV to the plasma membrane is severed. This involves the action of two proteins, Amphiphysin and Dynamin. Amphiphysin encodes two domains involved in this process, a BAR domain through which it dimerizes and binds the neck of the CCVand an SH3 domain used to recruit the GTPase enzyme dynamin. This binding activates Dynamin polymerization into a collar at the neck of the CCV and the specific localization of the GTPase action of dynamin leads to the membrane cleavage.

Following vesicle scission the endocytic vesicle quickly looses its clathrin coat, via the action of Hsp70 and the accessory protein auxilin. Clathrin may then be recycled for further use in a next round of endocytosis. The action of another accessory protein the lipid phosphatase, Synaptojanin, then converts PIP2 to Phosphatidylinositol, which further contributes to the uncoating of the vesicle of AP-2 and other bound accessory proteins. The endocytic vesicle then fuses with early endosomes to enable the internal sorting of its cargo, which will decide whether they are to be recycled or targeted for degradation. The membrane of the endocytic vesicle will ultimately be recycled back to the plasma membrane.

►Receptor Trafficking

Claude Syndrome

Definition

Claude syndrome results from unilateral ►tegmental lesion (infarction) of the ►midbrain and is characterized by oculomotor ►paresis and contralateral ►ataxia and ►tremor.

►Ataxia
►Tremor

Clausius-Duhem Inequality

Definition

A commonly accepted version of the second law of thermodynamics for continuous systems.

►Mechanics

Claustrum

Definition

The claustrum (Latin for fence or barrier) is a thin band of neurons positioned between the insula and the putamen (lateral part of the lentiform nucleus). Its principal connections are with the cerebral cortex; it has discrete inputs from somesthetic, auditory and visual cortices.

CLC Cl^- Channel/Transporter

Definition

A member of a related molecular family of Cl^- channels and transporters. This family is unique in that some members are bona-fide ion channels, transporting Cl^- down its electrochemical gradient through a continuous aqeous pore while others are Cl^-/H^+ antiporters, able to utilize the energy stored in the gradient of one of these ions to drive the other uphill, against its electrochemical gradient.

►Chloride Channels and Transporters
►Ion Transport

Clinical Gait Analysis

Definition

Procedure during which joint rotations, moments, and powers are collected along with electromyographic data

for purposes of clinical assessment and treatment decisions in patients with movement disorders.

►Motion Analysis

Clock

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Definition

CLOCK, an acronym for circadian locomotor output cycles kaput, is a basic helix-loop-helix, PAS domain-containing transcription factor considered a core element of both mammalian and *Drosophila* circadian clocks. CLOCK is one of two positive elements in the central ►feedback loop that defines the molecular clockwork. Protein products of the *Clock* (*Clk*) and *Brain muscle ARNT-like1* (►*Bmal1*) genes heterodimerize through interactions of PAS domains to form a complex that drives transcription of negative elements.

Characteristics

Discovery

Prior to the discovery of *Clock*, successful genetic approaches had been limited to identification of core circadian clock elements in *Drosophila* (►*Period* and ►*Timeless*) and *Neurospora* (*Frequency*). Attempts at cloning analogous genes in mammals were unsuccessful; the mammalian clockwork was truly a "black box." Although a genetic basis for mammalian circadian rhythmicity was indicated by the spontaneously occurring, semi-dominant mutation, *Bmal1* ►Tau mutation [1], the lack of knowledge regarding the hamster genome hampered efforts toward dissection of the molecular clock in this species. Positive identification of the first mammalian circadian ►clock gene, *Clock*, was finally accomplished using a forward genetic approach involving (i) isolation of circadian rhythm mutants following phenotypic analysis of *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis screens [2]; (ii) identification of affected genes using positional cloning and candidate gene methods [3]; and (iii) elucidation of gene function to understand their role in generation of circadian rhythmicity [4,5].

The initial ENU mutagenesis screen of 304 animals resulted in a single animal with phenotypic alteration of circadian period. This animal, the founder of the *Clock* mutant line, displayed an abnormally long circadian period under ►constant conditions. Further genetic analysis revealed a heritable, semidominant mutation involving alteration at a single locus. Heterozygous, *Clock*/+ mice, exhibit lengthened circadian periodicity under constant conditions. Mice homozygous for the ►*Clock* mutation, the *Clock* mutant mice (*Clock*/*Clock*), demonstrate an extreme lengthening of their endogenous period, and eventually these mice become arrhythmic. The single gene mutation in these mice has been mapped, by linkage analysis, to murine chromosome 5 [2]. The *Clock* mutant allele is an A → T nucleotide transversion that occurs at the third base position of the 5′ splice donor site of exon 19. The mutation causes production of an mRNA transcript that is missing exon 19. Although there is no change in reading frame, the mutant protein lacks 51 amino acids in the glutamine rich C-terminus domain [3]. The resulting protein is an antimorph, which acts in a dominant-negative fashion. The *Clock* mutant mice have provided a valuable tool for dissection of the molecular mechanisms of circadian rhythmicity in mammals.

Role of Clock in Regulation of Molecular Rhythmicity

Clock encodes a beta helix-loop-helix transcription factor that contains two PAS heterodimerization domains. CLOCK also has significant histone acetyltransferase activity [6]. It is a core component of the molecular mechanism that drives circadian rhythmicity in vertebrates, as well as in *Drosophila*. In mammals, *Clock* transcript and protein are constitutively expressed. Oscillations of its heterodimerization partner, ►BMAL1, confer circadian rhythmicity in transcriptional activity. In the *Drosophila* clock, however, CLOCK oscillates while CYCLE (*Drosophila* analog of BMAL1) remains constant. Binding BMAL1 enhances CLOCK's histone acetyl transferase activity, allowing chromatin remodeling to promote CLOCK:BMAL1 DNA binding [6]. CLOCK:BMAL1 heterodimers bind to E-box enhancer elements in the promoters of target genes to act as positive elements driving the molecular clock. CLOCK:BMAL1 activity is enhanced during late subjective night. Targets for CLOCK:BMAL1 include several clock genes, three-*Period*genes, two ►*Cryptochrome* genes and *Timeless*. As transcripts for these targets accumulate, they are translated, form heterodimeric complexes (primarily PER:CRY in mammals and PER:TIM in flies) and re-enter the nucleus where they act as negative elements to inhibit further transcription by CLOCK:BMAL1. Turnover of the negative elements allows CLOCK:BMAL1 activity to initiate a new cycle of transcription.

Physiological Relevance of CLOCK

The *Clock* mutant mice have been an invaluable tool for revealing the genetic underpinnings of circadian rhythmicity. Behavioral studies have demonstrated the importance of *Clock* in regulation of endogenous rhythms driven by the central oscillator in the

suprachiasmatic nucleus. *Clock* is important for regulating period length and for establishing stable persistence of behavioral rhythms.

More recent studies have focused on the role of the circadian clock in health and disease. A specific allele of *Clock* (3111C/C) is associated with evening preference in humans [7]. ►Delayed sleep phase syndrome, a circadian sleep-phase syndrome, in which individuals fail to adapt their sleep-wake cycle to environmental time cues, may be an extreme form of evening preference. *Clock* mutant mice also show rest/activity patterns consistent with delayed sleep phase syndrome, suggesting a role for *Clock* in regulation of the timing of sleep and wakefulness [8].

Polymorphisms in the 3′ flanking region of human *Clock* are associated with mania, insomnia and decreased need for sleep. *Clock* mutant mice, like bipolar patients in the manic state, are hyperactive and show increased responsiveness to the rewarding effects of psychostimulants. Treatment with the mood stabilizer, lithium, restores wild-type behavior. Thus, *Clock* may be an important regulator of brain neurochemistry associated with mood [9].

The circadian clock is central in control of energy balance. Disruption of the clock gene network, as occurs in the *Clock* mutant mice, leads to obesity and metabolic syndrome. Mutant mice have a severely disrupted diurnal feeding rhythm, which manifests as hyperphagia. Animals develop hyperlipidemia, hyperglycemia, hyperleptinemina and attenuated expression of several hypothalamic peptides associated with energy balance [10]. The fact that obesity does not result from a simple disruption of the circadian feeding pattern, or from mutation of other circadian clock genes, such as *Bmal1*, *Per1* or *Per2*, suggests that the *Clock* mutation may cause obesity in mice. Clearly, the circadian clock gene network in general, and the gene *Clock* in particular, are central to maintenance of health.

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Clock Cells

Definition

Cells that express endogenous circadian oscillations that regulate cellular functions and outputs.

►Cellular Clock
►Circadian Rhythm

Clock-Controlled Genes

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Synonyms

Circadian output genes

Definition

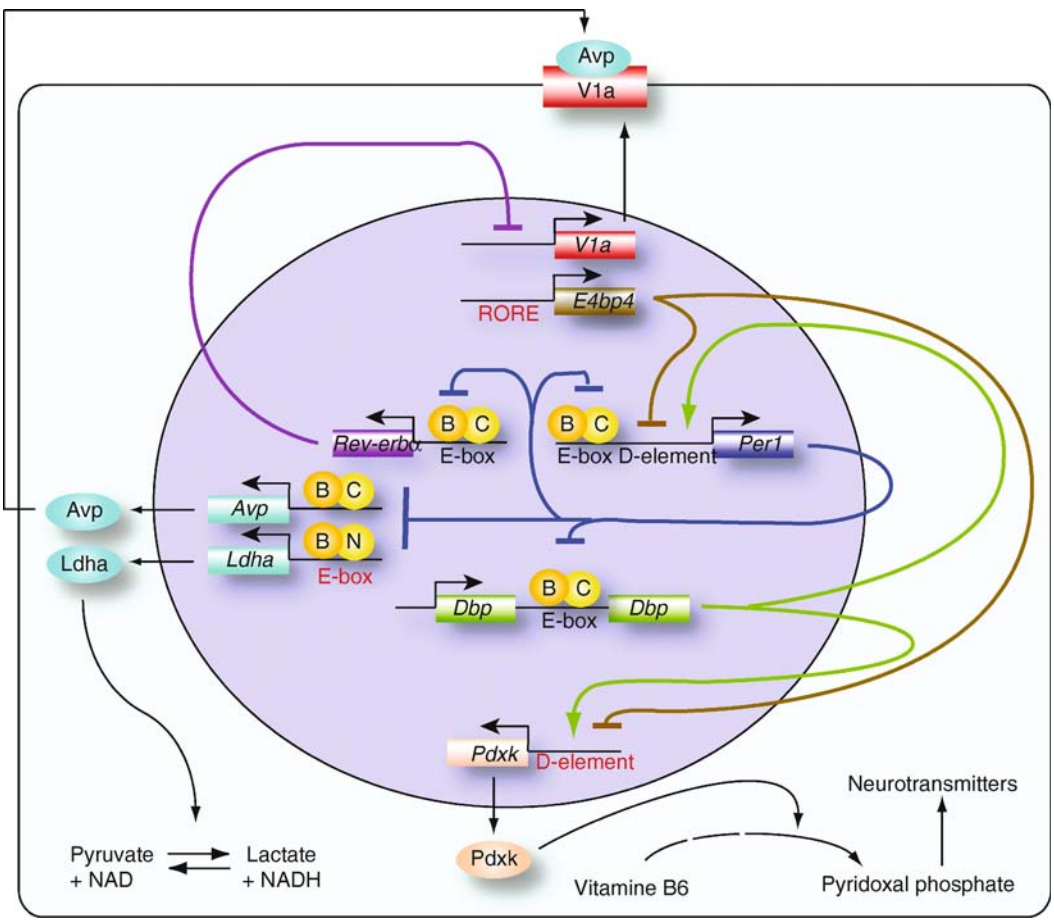
Genes whose time-of-day specific expression is dependent on the circadian oscillator.

Characteristics

The mammalian circadian oscillator is based on interconnected transcriptional and post-translational feedback loops. In the negative limb, transcriptional repressors of the ►Cryptochrome (Cry) and ►Period (Per) family periodically modulate the activation potential of the transcription factors Clock (or Npas2) and Bmal1 (see ►clock genes). By contrast, in the positive limb the orphan nuclear hormone receptors of the Rev-erb family repress transcription in the opposite phase of the negative limb. Both limbs together interact and govern oscillations of gene expression with a ►free-running period length of about a day. Due to the make-up of the circadian ►oscillator as transcriptional feedback loops, it is not surprising that most of the direct output is hardwired to the clock mechanism (Fig. 1).

A recent *in vitro* study combined with a systems biological approach came to the conclusion that the phase of circadian expression resulted from the utilization of three different types of response elements: ►E-box motifs as binding sites for Clock (or Npas2) and Bmal1, RORE motifs as binding sites for Ror and Rev-erb family members, and D-elements as binding sites for PAR bZip factors [1].

To address the question of how many *clock-controlled genes* exist, DNA microarray experiments have been conducted using the site of the central oscillator, the ►Suprachiasmatic nucleus (►SCN) in the brain as tissue source [2]. The obtained data were filtered afterwards to identify periodically expressed genes. Surprisingly, about 5% of the steady-state mRNA was rhythmically expressed with robust but sometimes low amplitude. This is still a rough estimate since the analysis of steady-state mRNA does not account for mRNA stability and many low-level cycling genes maybe eliminated artificially by the filters employed for data mining. The rhythmic genes



Clock-Controlled Genes. Figure 1 Clock-controlled genes are linked to the circadian oscillator. Circadian output genes are linked to the oscillator by E boxes, RORE, and/or D-elements. Per1 inhibits the activity of the Clock (C) or Npas2 (N) and Bmal1 (B) heterodimers. Lactate dehydrogenase A (Ldha) can affect the redox state of a cell, pydridoxal kinase (Pdxk) generates pyridoxal phosphate, a coenzyme involved in neurotransmitter synthesis, and arginine vasopressin (Avp) can bind rhythmically to its receptor V1a on SCN neurons. For details, see text.

identified included those for prohormone/neuropeptide synthesis, processing, and degradation, thought to be one of the main outputs of the SCN to govern the circadian rhythmicity of mammals. Some of these hormones, like ►pituitary adenylate cyclase-activating ►polypeptide *1* (►PACAP) and *arginine vasopressin* (*AVP*) had been known before as rhythmically expressed genes in the SCN. Another important set of coordinately expressed genes contained enzymes important for carbon source utilization and oxidative phosphorylation in the mitochondria. The detailed analysis of this pathway suggested a circadian rhythm in the energy metabolism and redox state of SCN neurons.

A major surprise was the relatively small overlap of rhythmic transcripts between different tissues examined. In the study by Panda et al. [2], about 330 rhythmic transcripts specific for either the SCN region in the brain, or the liver were found and there were only 28 overlapping transcripts, which included most core oscillator components. Therefore, the output genes are not only subject to circadian control of gene expression, but also to tissue-specific control. At the moment, we have much better insight into the circadian control than the tissue-specific control of circadian output genes. However, it appears that both components together are necessary to orchestrate the expression of genes in a manner optimal for a specialized tissue such as the SCN. In the context of this essay we will focus on known *clock-controlled genes* in the brain.

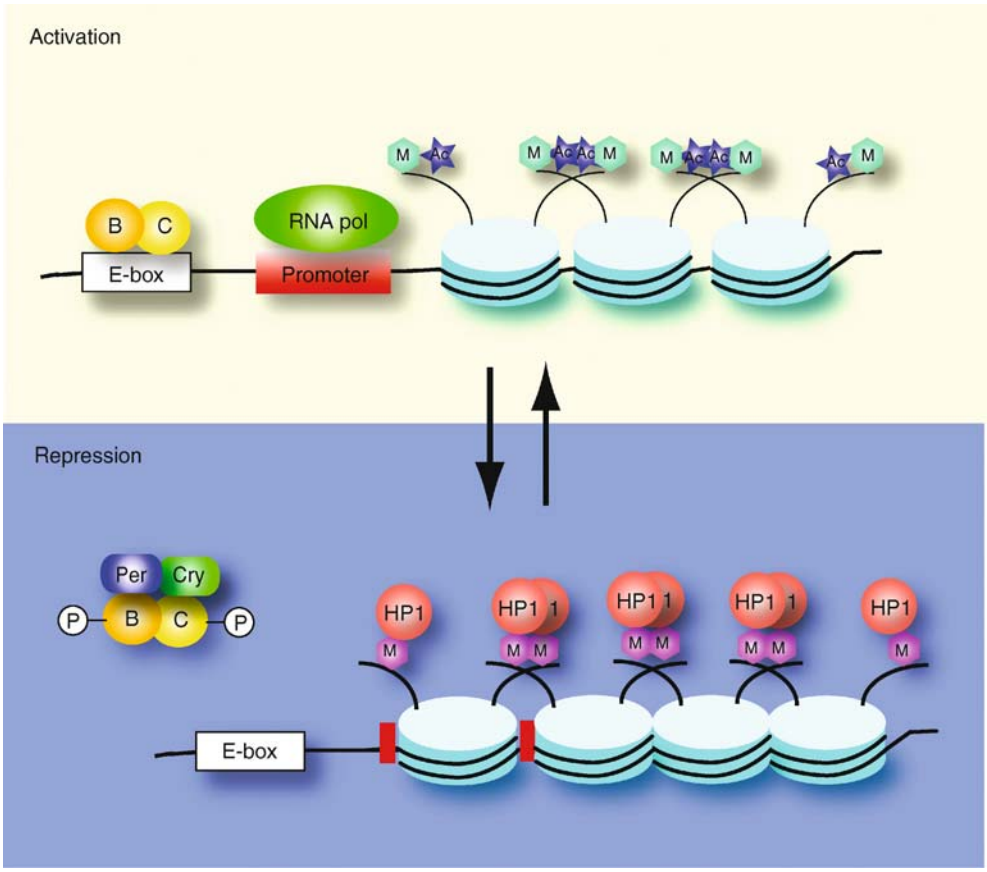
The first gene to be analyzed in great detail and linked to the molecular oscillator was the *arginine vasopressin* gene ([3], Fig. 1). This hormone is synthesized mainly in the vasopressinergic neurons of the paraventricular nuclei (PVN) and the *Supraoptical nuclei* (SON). It is released into the bloodstream from the posterior pituitary to regulate the salt and water balance. However, this hormone acts also as a neuropeptide in the *central nervous system* (CNS). For instance, it is rhythmically produced by the neurons of the SCN and modulates the firing rate of SCN neurons in a very local fashion. The expression of this gene was nearly abolished in the SCN but not in the SON of *ClockΔ19/ClockΔ19* homozygous mutant mice, which carry a dominant-negative version of the Clock protein. Subsequent analysis revealed the importance of the E-box motif in the promoter region of this gene as a binding site for Clock and Bmal1. Altogether, the data suggested that the *arginine vasopressin* gene was directly hardwired to the molecular oscillator via its E-box motif and the transcriptional activators Clock and Bmal1. Interestingly, in the SON region there were barely detectable levels of Bmal1, and this may impair an effect of the ClockΔ19 mutation on the transcription of this gene. However, it is still an unresolved issue, why the expression of this gene is so highly specific for the CNS.

The transcription factor *D-site binding protein* (Dbp) was originally thought to manifest a liver-specific regulator of the *albumin* gene. However, it was identified as a ubiquitous output gene expressed with very high circadian amplitude. Mice deficient of this gene display a 30 min shorter free-running period length indicating a feedback of this protein to the circadian oscillator. As a rhythmically expressed transcription factor, Dbp can amplify the action of the circadian oscillator on many D-element bearing target genes (Fig. 1). In triple knock out mice with an inactivation of the *Dbp* gene and the two other members of the PAR bZip transcription factors, sporadic and audiogenic epileptic seizures occurred [4]. This phenotype was linked to a slight deregulation of the gene for pyridoxal kinase (*Pdxk*), involved in the pathway for the conversion of vitamin B6 derivates into pyridoxal phosphate. Pyridoxal phosphate is a coenzyme of many enzymes involved in the metabolism of various neurotransmitters. This is an example of a very drastic phenotype provoked by a subtle deregulation of an enzymatic activity. Thus, subtle circadian changes in enzymatic activities can have a drastic influence on physiology and metabolism.

The circadian regulation of the *Dbp* gene was analyzed in great detail in the liver but the mechanism is probably very similar for the SCN ([5], Fig. 2).

The transcription cycle of *Dbp* is initiated by binding of Clock and Bmal1 to three defined E-box containing regions within the gene. The binding of these factors provokes a change in the local chromatin structure as evidenced by the acetylation of lysine 9 of histone H3, the trimethylation of lysine 4 of histone H3, and a reduction of the histone density overall. Under these conditions transcription of the gene commences. After a certain time, Clock and Bmal1 fall off their target sites within *Dbp*, the transcription ceases, and the chromatin closes in to form a heterochromatin-like, inactive state. Upon re-binding of Clock and Bmal1 the next day, another circadian cycle can start. While *Dbp* is expressed in the liver and the SCN neurons with very high circadian amplitude, its amplitude of cycling in the other parts of the brain is much lower, indicating some additional tissue-specific component.

Npas2 is an analog of Clock expressed mainly in the forebrain. To address the regulatory potential of this transcription factor, an inducible neuroblastoma cell line for Npas2 and Bmal1 was engineered. One surprising target gene upregulated after the induction of these transcriptional regulators was the *A isoform of lactate dehydrogenase* (*Ldha*) ([6], Fig. 1). This enzyme reversibly catalyses the dehydrogenation of pyruvate to lactate. Therefore, it has a direct impact on the redox state within a cell by influencing the ratio of reduced nicotinamide adenine dinucleotide (NADH) to its oxidized form, NAD. Astonishingly,



Clock-Controlled Genes. Figure 2 Rhythmic binding of Clock (*yellow*) and Bmal1 (*orange*) to DNA governs circadian *Dbp* transcription and chromatin transitions. During active transcription there are less histones (*light blue discs*) around the promoter (*red rectangle*), and they are marked by acetylation of lysine 9 (*blue stars*) of histone H3 and trimethylation of lysine 4 (*teal hexagons*) of histone H3. During repression, the heterochromatin closes as a consequence of change in methylation (*pink hexagons*), binding of heterochromatin binding protein 1 (HP1, *rose circles*) and loss of acetylation of histones. The promoter (*red*) is packed by histones (*blue disc*) and the transcription shuts off. The chromatin transitions and the transcription are dependent on rhythmic Clock and Bmal1 binding. Light yellow background represents activation during the day, whereas blue shows repression during the night.

the heterodimer formation between Npas2 and Bmal1, and the binding activity of this heterodimer to DNA were both dependent on the ratio of NADH to NAD: the reduced form repressed heterodimer formation and concomitantly DNA binding of the heterodimer. This led to an interesting but still preliminary model of entrainment of neurons by changes in the redox state of neurons: in a first step, astrocytes take up extra-cellular glutamate from the synaptic clefts secreted during neuronal activity. This stimulates glycolysis in these cells and subsequently the secretion of lactate. The lactate is taken up by the neurons again and provokes circadian fluctuations of the redox state that govern the activity of the NPAS2 and BMAL1 heterodimers. This may in turn rhythmically affect the neuronal activity and therefore the periodic secretion of glutamate.

After these examples of *clock-controlled genes* that are direct targets of activation by Clock (or Npas2) and Bmal1, we now turn towards genes that contain binding sites for the transcriptional repressors of the Rev-erb family (Fig. 1). The function of ROREs within the circadian clock was found by two independent approaches: (i) the circadian amplitude of the expression of *Bmal1* in the SCN and liver of ►*Rev-Erbα* homozygous knock out mice was severely dampened [7]; (ii) in a DNA microarray study the circadian transcripts of SCN and liver were grouped according to their phases of expression, then the transcription start sites were identified, and the promoter regions subsequently analyzed for common binding motifs for transcriptional regulators [8]. The target genes identified in this fashion included *Bmal1*, *E4bp4*, and the *arginine vasopressin receptor 1A* (*V1a*). Interestingly,

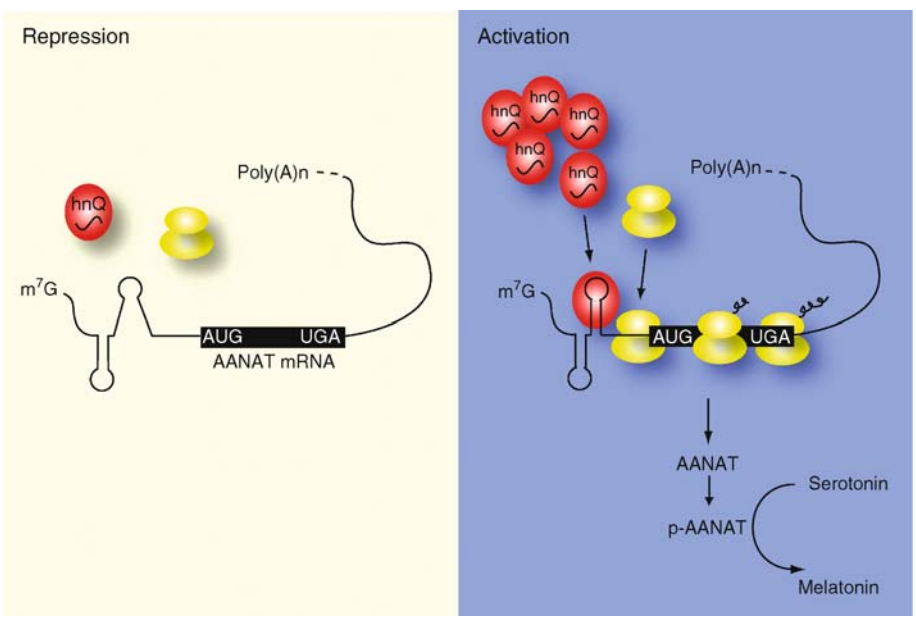
E4bp4 is a repressor of transcription with the same DNA binding specificity as the PAR bZip transcription factors that become expressed in the opposite phase. It is tempting to speculate that a particular target gene can alternatively bind PAR bZip transcription factors or the repressor E4bp4, allowing precise transcriptional regulation. Circadian expression of the V1a receptor was also an interesting finding since its ligand arginine vasopressin is expressed in a different phase in the SCN neurons (see above).

A completely different kind of circadian regulation is found in the ▶pineal gland regarding the translation of the rate-limiting enzyme in melatonin synthesis, the arylalkylamine N-acetyltransferase (AANAT) ([9], Fig. 3).

In rodents, the peaks of mRNA and protein accumulation are separated by four to six hours. This delay is due to a co-translational regulatory mechanism. The 5′-untranslated region of the mRNA contained an *internal ribosome entry site* (IRES), which allowed 5′-Cap independent translation. However, this particular IRES permitted the translation of the mRNA only in the presence of sufficient amounts of *Heterogeneous nuclear ribonucleoprotein Q* (*hnRNP Q*). This protein bound specifically to the IRES sequence of AANAT and recruited the ribosome complex to initiate the translation. HnRNP Q accumulated in the nuclei of pinealocytes in a circadian fashion, gating the translation of the AANAT mRNA to a specific time-window. It is tempting to speculate that this complicated mechanism of co-translational regulation is a rather widespread phenomenon within the mammalian circadian oscillator.

Taken together, *clock-controlled genes* within the CNS and other tissues are controlled by different mechanisms. The simplest fashion is a direct coupling of the target genes to the core oscillator via Clock (or Npas2) and Bmal1, or the Rev-erb family. A more indirect way exploits various transcriptional regulators, e.g., Dbp and E4bp4, as intermediaries. Maybe this could account also for the differences observed in the circadian clocks of different tissues. One should keep also in mind that changes in the transcriptional status of a gene not necessarily reflect drastic changes in the protein levels, and vice versa (see the co-translational mechanism).

Where does the research go? Many mental syndromes like depression, mania, and bipolar disorder are somehow linked to the circadian clock. Therefore, it is an important task to identify potential target genes whose unbalanced circadian expression interferes with the normal health status. However, this task is by far not an easy one, since even subtle changes in the level of neurotransmitters might have drastic effects as seen, for example, for the pyridoxal kinase. Another example concerns the influence of the clock gene *Per2* on



Clock-Controlled Genes. Figure 3 Co-translational regulation of the arylalkylamine N-acetyltransferase (AANAT) gene in the pineal gland important for melatonin production. High amounts of HnRNP Q protein are necessary to bind to an IRES sequence within the 5′-untranslated region of the AANAT mRNA to allow for the formation of active translation complexes to initiate the production of AANAT protein. Upon phosphorylation (p-AANAT) serotonin is converted to melatonin. Light yellow background represents repression during the day, whereas blue shows activation during the night.

alcohol consumption [10]. In *Per2* ^{Brdm1} homozygous mutant mice, the expression of an astrocyte-specific glutamate transporter is slightly down regulated, provoking a hyper-glutamatergic state within the CNS. As a consequence, the animals consume more and are more resistant to alcohol. The effect of the *Per2* mutation can be reverted by the application of acamprostate, a drug that is thought to act by dampening a hyper-glutamatergic state. As an estimate, 10% of alcoholic patients respond well to this drug. In the future, with a more detailed knowledge of the circadian oscillator of the CNS and its target genes, it will be possible to understand and to develop new therapies that will help to treat mental disorders.

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Clock Coupling Factors

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Definition

In this essay, the term "clock coupling factors" is understood in two ways: (i) factors by which the circadian pacemaker in the suprachiasmatic nucleus (SCN) of mammals controls circadian behavioral rhythms and (ii) factors that synchronize the cellular clocks within the SCN to enable a coherent rhythmicity of the SCN tissue.

Characteristics

Candidate Factors That Couple the Clock to Locomotor Activity Rhythms

The mammalian circadian clock residing in the ►suprachiasmatic nucleus (►SCN) is thought to drive circadian rhythms of locomotor behavior by secreting diffusible factors that act locally within the hypothalamus. This concept is primarily based on SCN transplant experiments: when fetal SCN tissue is transplanted into animals made arrhythmic by lesion of the SCN, circadian rhythms of locomotor activity are restored with the period of the donor tissue [1]. This occurs even when the graft is encapsulated to prevent extension of axons but allow diffusion of secreted factors [2]. These results demonstrate that in the transplanted animal the SCN secretes "locomotor factors" that reach their targets by diffusion in a paracrine fashion. Hamsters with functional SCN tissue of both wild type and short-period mutant (►tau-mutation) genotypes ("temporal chimeras") displayed locomotor activity rhythms influenced by the oscillators of both genotypes. While there was no evidence of coupling between the two underlying oscillators, locomotor activity was suppressed at times when the ►rest phase (►rho) of one influence intersected with the ►activity phase (►alpha) of the other, indicating that the SCN inhibits locomotor activity at one phase and probably promotes it at another, with inhibition dominating when the two influences coincided [3]. Three factors have been identified that strongly inhibit locomotor activity when injected or infused into the third ventricle of the hypothalamus, i.e. ►transforming growth factor alpha (►TGF-α) [4], ►prokineticin 2 (PK-2) [5] and cardiotrophin-like cytokine (CLC) [6]. So far, no SCN factor promoting activity has been proposed.

TGF-α is expressed in the SCN in a circadian fashion, and, when infused into the third ventricle, reversibly inhibits locomotor activity and disrupts circadian

sleep-wake cycles. These actions are likely mediated by epidermal growth factor (EGF) receptors on neurons in the hypothalamic ►subparaventricular zone, a major relay station for SCN efferents. Mice with a hypomorphic EGF receptor mutation exhibit excessive daytime locomotor activity and fail to efficiently suppress activity when exposed to light (so-called "►masking") [4].

PK2's rhythmic expression in the SCN is directly mediated by ►CLOCK-►BMAL1 activity acting on E-box enhancer elements in the promoter of the PK2 gene (see ►Clock-controlled genes). Receptors for PK2 are abundantly expressed in major target nuclei of the ►SCN output pathway. Intracerebroventricular infusion of PK2 at night, when endogenous PK2 mRNA levels are low, markedly reduces the nocturnal increase in locomotion. Mice with a disruption of the PK2 gene display significantly reduced rhythmicity for a variety of circadian physiological and behavioral parameters including sleep-wake cycle, locomotor activity, body temperature, and circulating glucocorticoid as well as glucose levels [5].

CLC is rhythmically expressed in a small subpopulation of vasopressin containing SCN neurons with a peak in the ►subjective day. CLC receptors flank the third hypothalamic ventricle and acute infusion of CLC into the third ventricle results in a reversible inhibition of locomotor activity without affecting the circadian clock. Infusion of CLC receptor neutralizing antibodies produces access locomotor activity at a time when CLC is maximally expressed [6].

Together, these results suggest that the aforementioned SCN signals may provide a crucial link between the circadian clock and outputs by shaping daily rhythms of behavior.

Candidate Factors That Synchronize the Cellular Oscillators Within the SCN

SCN neurons generate endogenous circadian rhythms endogenously and adjust them according to the ►light-dark cycles of the environment (►entrainment). SCN neurons dispersed in cell culture display cell-autonomous oscillations with periods ranging from 20 to 28 h. Despite of this broad distribution of ►free-running periods of isolated neurons, the oscillation of the 20,000 ►SCN neurons *in vivo* (see also ►Multi-oscillator system) is coherent and ►self-sustained (►oscillation) with an average period of about 24 h indicating that a coupling mechanism is operating between the SCN neurons. Without such an intercellular communication – e.g. when action potentials are blocked with tetrodotoxin (TTX) - synchrony between rhythmic SCN neurons is lost. In addition, at least some neurons lose rhythmicity on the cellular level suggesting that synchrony among neurons is a prerequisite for self-sustained ►rhythmicity in some cases. Criteria for being a candidate synchronizing factor are: (i) expression in SCN ►pacemaker neurons, (ii) circadian activity, and (iii) expression of the respective receptor in the SCN (for a review see [7]).

Up to now, the strongest putative candidate synchronization factor is the neuropeptide vasoactive intestinal polypeptide (VIP), because it meets many of the above mentioned criteria. VIP is synthesized in the ventrolateral part of the SCN, VIPergic neurons project densely within the SCN, VIP is rhythmically released from rat SCN *in vitro*, its receptor VPAC2 is expressed in about 60% of all SCN neurons, and VIP pulses phase-shift the circadian clock of the SCN. Targeted disruption of the genes coding for VIP or its receptor results not only in a loss of synchrony between SCN neurons but also in the arrhythmicity of most of the SCN neurons [8,9]. These results suggest that VIPergic signaling serves two functions in the SCN: promoting rhythmicity in a subset of non-pacemaking SCN neurons, and synchronizing pacemaking neurons.

Among other synchronizing factor candidates (for a review see [7]) are the neurotransmitters gastrin-releasing peptide (GRP) and prokineticin 2, whose expression patterns, as well as that of their receptors, are compatible with a putative role in synchronization. Furthermore the neurotransmitter GABA has been suggested as a putative synchronizing factor. GABA, as well as the $GABA_A$ and $GABA_B$ receptors, are expressed abundantly throughout the SCN and there is evidence for a circadian release of GABA. Moreover, it has been reported that GABA application can ►phase-shift the electrical activity of SCN neurons *in vitro*. In addition, signals using the G-protein subunits Gi/o [10] as well as gap junctions have been implicated in the intra-SCN synchronization mechanism. However, with the exception of VIP, the aforementioned candidates are far from being established as synchronizing factors within the SCN, and more work needs to be done to evaluate their individual contribution to SCN synchrony.

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Clock Genes

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Synonyms

Circadian clock genes

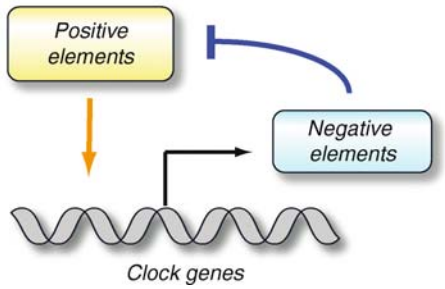
Definition

Any of a number of genes that interact with each other to make up an auto-regulatory feedback loop, in which its activation and repression cycle takes about one day.

Characteristics

Clock genes are components of the circadian clock comparable to the cogwheels of a mechanical watch. They interact with each other in an intricate manner generating oscillations of gene expression. The underlying principle of circadian clocks is successive gene activation in the form of a cycle: the initial activation of a gene is regulated by the last one in the sequence, making up an auto-regulatory feedback loop for which one cycle takes about 24 h. This principle is illustrated in Fig. 1.

Positive elements activate the expression of negative elements, which in turn stop the activity of the positive elements. This system moves away from equilibrium before returning and hence, perpetual cycling is the consequence. Although the genes involved in this mechanism can differ in various organisms, the principle illustrated in Fig. 1 is common to all of them (reviewed in [1]).



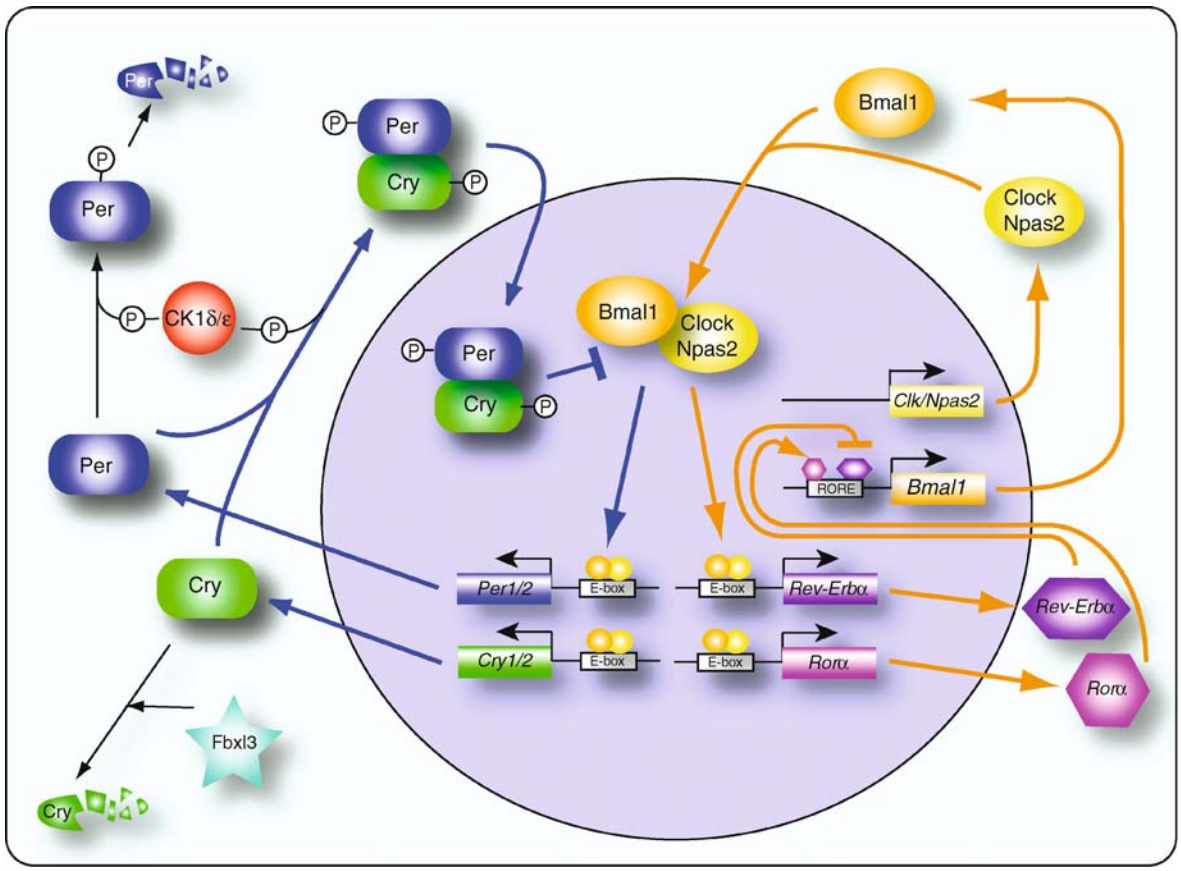
Clock Genes. Figure 1 General principle of the transcriptional autoregulatory feedback-loop. This principle underlies the clock mechanism in organisms that have a circadian clock.

In mammals the circadian clock mechanism is made up of two interlocking, regulatory feedback loops (Fig. 2, orange and blue lines).

In the first loop (blue lines), two transcriptional activators ►Bmal1 (brain and muscle ARNT-like protein 1) and ►Clock (or Npas2 in neuronal tissue) form heterodimers in the cytoplasm and enter the nucleus where they bind to ►E-box sequences in the promoters of ►Period (*Per1,2*) and ►Cryptochrome (*Cry1,2*) genes contributing to the activation of their expression. In the cytoplasm various combinations of Per and Cry proteins interact with each other, enter the nucleus and inhibit the activity of Bmal1/Clock or Bmal1/Npas2 complexes. Without these complexes activating transcription of the *Per* and *Cry* genes, levels of *Per* and *Cry* transcripts and their respective protein products decline, hence *Per* and *Cry* genes shut off their own transcription (reviewed in [2]).

A second loop regulates the expression of the *Bmal1* gene (orange lines, Fig. 2). In the nucleus Bmal1/Clock or Bmal1/Npas2 heterodimers bind to E-boxes present in the promoters of genes that encode the retinoic acid-related orphan nuclear receptors ►Rev-erbα and ►Rorα, which compete for the ROR element (RORE) in the *Bmal1* promoter. Rorα activates *Bmal1* expression, while Rev-erbα represses it. As a consequence oscillations of *Bmal1* and *Rorα/Rev-erbα* are out of phase. If activation wins over expression Bmal1 protein is produced and it forms heterodimers in the cytoplasm with Clock or Npas2 depending on the tissue [3]. These heterodimers enter the nucleus and initiate the next cycle of gene activation of both loops. The regulation of Clock and *Npas2* is at present not understood.

How do Bmal1 and Clock contribute to the activation of transcription of other clock genes? It appears that transcriptional activation is facilitated by the histone acetyl transferase (HAT) activity of the Clock protein [4]. Histone acetylation promotes transcription through the modification of histones (Ac, Fig. 3) and allows



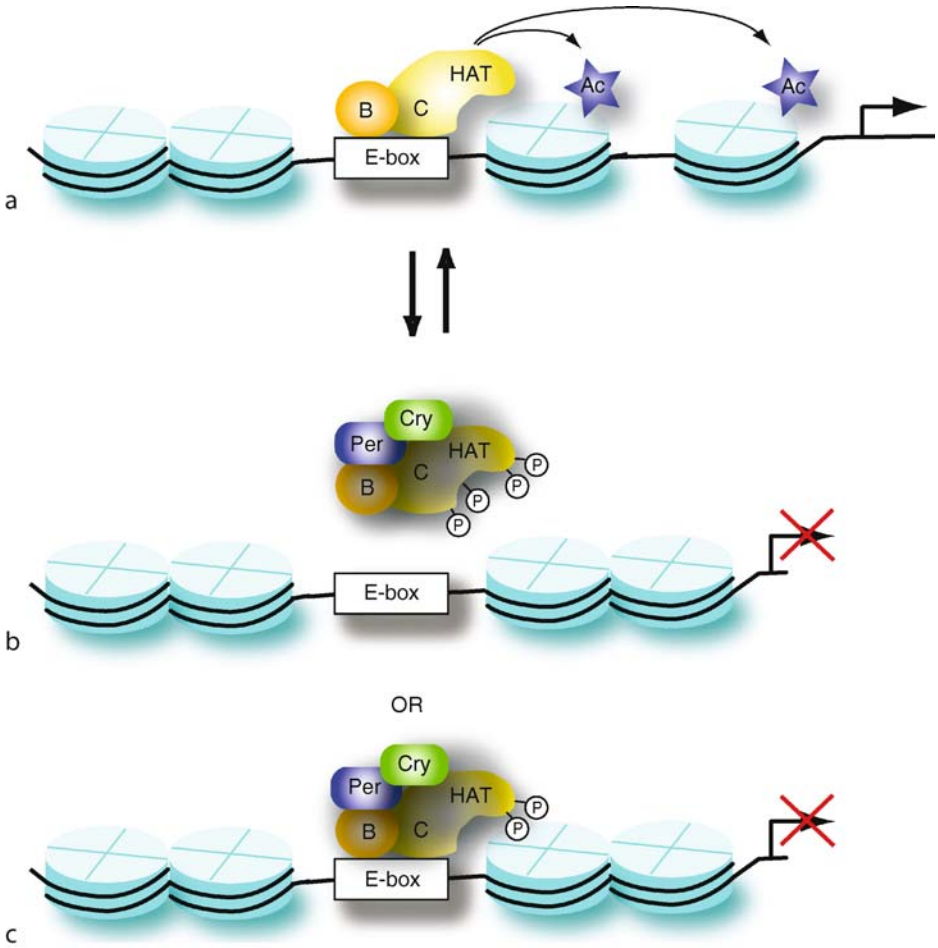
Clock Genes. Figure 2 Hypothetical clock mechanism in mammals. Note the two loops (*blue lines* and *orange lines*) converging on the transcriptional activators Bmal1 and Clock/Npas2. Besides transcription, nuclear import of clock factors and posttranslational modification of these factors (such as phosphorylation, circled P in diagram) seem to play an important role in the regulation of the feedback-loop. For details see text.

opening of the condensed chromatin. This provides access to the transcriptional machinery (Fig. 3, RNA Polymerase II and general transcription factors).

The HAT activity of Clock is necessary for the transcriptional activation of the clock genes *Per* and *Cry* and therefore seems to be essential for the generation and maintenance of endogenous circadian rhythms in mammals. Transcriptional repression is mediated by several events. Per and Cry bind to the Bmal1/Clock complex. This results in loss of HAT activity of Clock by promoting Clock phosphorylation (P) and/or inducing a conformational change of Bmal1/Clock. Whether these changes induced by Per and Cry leave Bmal1/Clock bound to the E-box or cause dissociation from it is not known. In either case, loss of Clock HAT activity promotes histone deacetylation. This prevents the general transcription machinery from binding to DNA and hence transcription is repressed. Upon degradation of Per and Cry, Clock is either dephosphorylated or degraded and resynthesized. It then interacts again with Bmal1 and acetylates histones to activate a new transcription cycle.

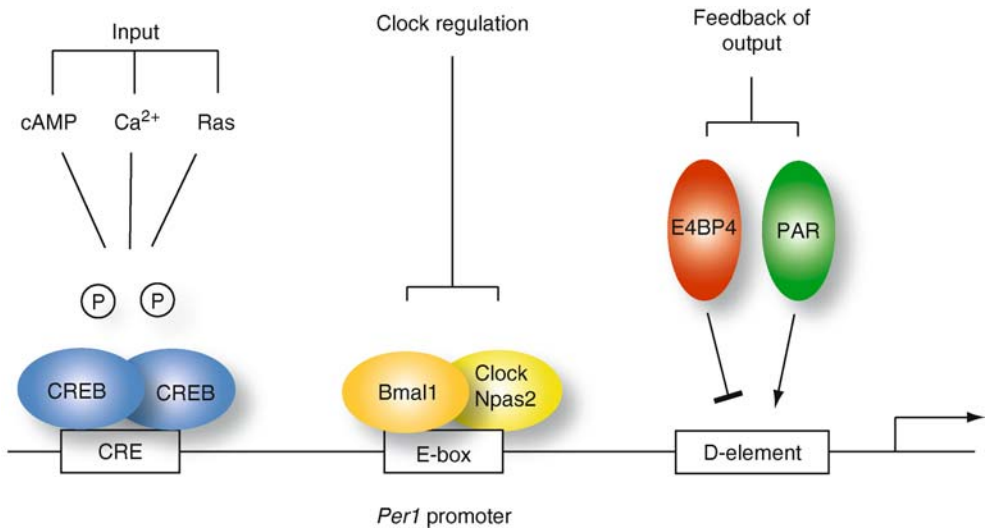
Clock gene expression regulated exclusively by transcriptional processes would run into equilibrium and no oscillation of gene expression would be observed. Transport of clock proteins from the cytoplasm into the nucleus as well as posttranscriptional processes are additional levels of regulation of the clock mechanism for generating oscillations of approximately 24 h. Per and Cry proteins interact with each other which prevents rapid degradation of these proteins and enables them to enter the nucleus. Mutation of interaction sites in either Per or Cry protein disturbs the nuclear and cytoplasmic localization with consequences on the clock oscillator (reviewed in [2]).

Phosphorylation and dephosphorylation of proteins is a widely used mechanism to regulate protein stability, activity, and structure in many biological processes such as signal transduction. In the generation of mammalian circadian rhythms phosphorylation and



Clock Genes. Figure 3 Diagram depicting the histone acetyltransferase (HAT) activity of Clock (*yellow*). (a) Acetylation (Ac, *blue stars*) of histones (*light blue discs*) near the promoter region of target genes greatly facilitates transcription by RNA polymerase II. Upon binding of Per/Cry, Clock is phosphorylated which either leads to detachment of the complex from the E-box (b) or simply inactivates HAT activity (c) leading to inactivation of transcription (*red crosses*).

dephosphorylation of Per proteins plays a critical role in determination of period length. For example, casein kinase 1 ε or δ (CK1ε/δ, Fig. 2) phosphorylates Per2 protein at different sites. If predominantly amino-terminal sites are phosphorylated, Per2 protein will be degraded. However, if sites in the second part of the Per2 protein sequence are phosphorylated, Per2 is stabilized and can interact with Cry proteins to enter the nucleus and interfere with the Bmal1/Clock or Bmal1/Npas2 complexes (Fig. 2) (reviewed in [5]). Interestingly, mutations in the CK1ε as well as in sites of Per2 that are important for CK1ε binding and phosphorylation cause alterations in period length. Patients with a specific form of familial advanced sleep phase syndrome have the mutation S662G in their PER2 protein, leading to a loss of binding of casein kinase 1ε/δ (CKIε/δ) and hypo-phosphorylation of PER2 [6]. This leads to a shortened period length of the circadian clock and hence these patients have an accelerated clock. As a consequence they display a 4-h advance of the daily sleep-wake rhythm. *In vitro* studies and mouse genetics revealed that alteration of the serine at position 662 in mouse Per2 recapitulates the finding in humans. Furthermore a change from S to D, mimicking by its constitutive phosphorylation and allowing constitutive binding of CKIδ, increased phosphorylation of Per2 leading to a longer period length (reviewed in [5]). This indicates the importance of regulation of clock proteins to specify period length. Therefore it is not unexpected that Cry also is regulated by CK1ε/δ. Furthermore, Cry abundance is regulated by its interaction with Fbxl3, a subunit of one of more than 70 mammalian ubiquitin ligase complexes that recognizes targets for degradation by the proteasome, a multisubunit molecular protein shredding machine (reviewed in [7]). Upon binding of Cry to Fbxl3 it becomes ubiquitinated and is degraded



Clock Genes. Figure 4 Regulatory elements in the promoter of the clock gene *Per1*. Besides regulation by clock factors through E-boxes, activation of the input pathway for example by light leads to changes in various signaling pathways converging on the CRE-element. Also clock-controlled genes can feed back and influence clock gene expression by binding to D-elements either activating (PAR leucine zipper transcription factors such as Dbp) or inhibiting (E4BP4) transcription.

by the proteasome. It appears that circadian oscillations are tuned by a delicate ratio of Per and Cry proteins, whose levels are regulated by phosphorylation and ubiquitination. If their relative abundance is changed, alterations in the clock oscillator are the consequence [8].

The circadian clock is not only a timekeeper. To serve as a predictor of recurring events in nature it needs to have the potential to adapt to changes in lighting and feeding conditions. Therefore clock genes not only respond to regulators of the clock mechanism described in Fig. 2, but also to signaling pathways that connect the organisms biochemical organization with timed events in the environment (reviewed in [9]). Signals such as light stimulate cellular changes in calcium and cAMP levels which lead to phosphorylation of the cAMP responsive element binding protein (CREB) that homodimerizes and binds to the cAMP responsive element (CRE) in the promoter of some clock genes such as *Per1* (Fig. 4).

This causes fast induction of transcription of this gene leading to an adjustment of the circadian clock. Transcription factors, such as E4BP4 and Dbp (PAR leucine zipper transcription factor) are regulated by nutritional cues and the clock (see ▶clock-controlled genes). Through binding to the D-element in the promoter of clock genes such as *Per1* they either stimulate (Dbp) or repress (E4BP4) transcription [10]. In this way, the metabolic state of an organism is reported back to the clock (Fig. 4, feedback of output). Hence, clock genes are not only generating a circadian rhythm but also integrate the metabolic state of the organism and information from the environment.

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Clock Mutation

Definition

An alteration of the circadian clock gene identified as circadian clock output cycles kaput. The Clock mutation, discovered through an N-ethyl-N-nitrosourea mutagenesis screen, was the first circadian clock gene to be identified in mammals. The mutant allele is a 5' splice donor mutation that skips exon 19, thereby producing a form of CLOCK protein that is missing 51 amino acids from the C-terminal activation domain.

The resulting protein is an antimorph, which acts in a dominant-negative fashion. The mutated CLOCK protein retains the ability to form PAS-domain dependent heterodimers with BMAL1. Although heterodimers formed between BMAL1 and mutated CLOCK also retain their DNA-binding capabilities, transcriptional activation is deficient. Animals bearing a mutation of the Clock allele display lengthened periodicity, and ultimately, failure in expression of behavioral circadian rhythms.

►Cellular Clock
►Circadian Rhythm
►Clock-controlled Genes
►Clock Genes

Clonus

Definition

Oscillatory muscle contraction at about 4-6 Hz. It is considered to result from increased stretch-reflex excitability, caused by sufficient muscle stretch and increased spinal cord excitability, in particular in ►spasticity.

►Spasticity

Closed-loop Behavior

Definition

Behavior in which the consequences of the actions have an influence on the sensory input. Under normal conditions behavior is closed loop. The loop may be opened by an experimenter. There are also natural situations that resemble an open loop: when the stimulus is over before the reaction starts (see also open-loop behavior).

Cluster Headache

Definition

An excruciating, primary headache lasting 15 min to 3 h. It is unilateral, orbital, supraorbital, or temple pain accompanied by autonomic features.

►Headache

CNG channels

►Cyclic Nucleotide-Regulated Cation Channels

CNS Demyelinating Disease

Definition

Demyelination is myelin loss with relative preservation of axons. The central nervous system (CNS) is composed of the brain and the spinal cord. The most common CNS demyelinating disease in humans is multiple sclerosis. Demyelinating diseases do not include genetic disorders of myelin formation (dysmyelination) or diseases causing myelin destruction secondary to neuronal death and Wallerian degeneration, such as amyotrophic lateral sclerosis and spinal cord injury.

►Amyotrophic Lateral Sclerosis (ALS)
►Multiple Sclerosis
►Wallerian Degeneration

CNS Germinal Niche

Definition

Specialized central nervous system (CNS) microenvironment in which neural stem cells reside and support self-renewal and differentiation (neuro- and gliogenesis). Environmental cues and intrinsic genetic

programs are required to maintain stem cell properties within CNS germinal niches. The subventricular zone (SVZ) of the lateral ventricle wall and the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus are two major brain germinal niches in the adult mammalian life. Cells with structural and molecular characteristics of astrocytes [immunoreactive for glial fibrillary acidic protein (GFAP)] are the true stem cells (or type B cells) in the SVZ and SGZ. GFAP+ astrocytes are in intimate contact with all other SVZ cell types, including type C cells (rapidly dividing transit amplifying cells) and the type A cells (lineage-committed post-mitotic migratory neuroblasts). Type B cells in the SVZ are in close contact (e.g., interdigitated) with both the BL and the blood vessels. The cell lineage differentiation pathway goes from type B, through type C to type A cells, with type B cells believed to be the self-renewing primary precursors.

GFAP+ astrocytes also function as stem cells (type B cells) in the SGZ, undergo self-renewal, proliferation and differentiation into transit amplifying cells (type D cells) and then into lineage-committed migratory granule neurons (type G cells). In the SGZ, bursts of endothelial cell division are spatially and temporally related to clusters of neurogenesis. Stem cell maintenance within CNS germinal niches appears to be dependent on stem cell physical contact to the basal lamina (BL) which acts as a scaffold concentrating and/or modulating cytokines/growth factors derived from local cells (e.g., fibroblasts, macrophages, pericytes, etc.).

►Autoimmune Demyelinating Disorders: Stem Cell Therapy
►Stem Cell

CNTF

Definition

►Ciliary Neurotrophic Factor

Co-activation

Definition

Simultaneous activation of skeletomotor and fusimotor neurones.

►Proprioception Roles of Muscle Receptors

Co-activation, Co-activation Zone

Definition

A range of positions of a joint or body segments within which opposing groups of muscles are co-active; threshold control is responsible for the extent and localization of the zone(s).

►Equilibrium Point Control

Coarticulation

Definition

Phenomenon in speech whereby attributes of successive speech units overlap in articulatory or acoustic patterns.

►Speech Perception

Cocaine

Definition

Cocaine is a stimulant drug that increases brain extracellular levels of the neurotransmitters dopamine, serotonin, and noradrenaline by inhibiting the monoamine neurotransmitter transporters.

►Stimulants

Coccus

Definition

A (roughly) spherical bacterium, with two bundles of short flagella near one pole of the cell.

►Magnetic Bacteria

C

Cochlea

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Synonyms

Acoustic Labyrinth

Definition

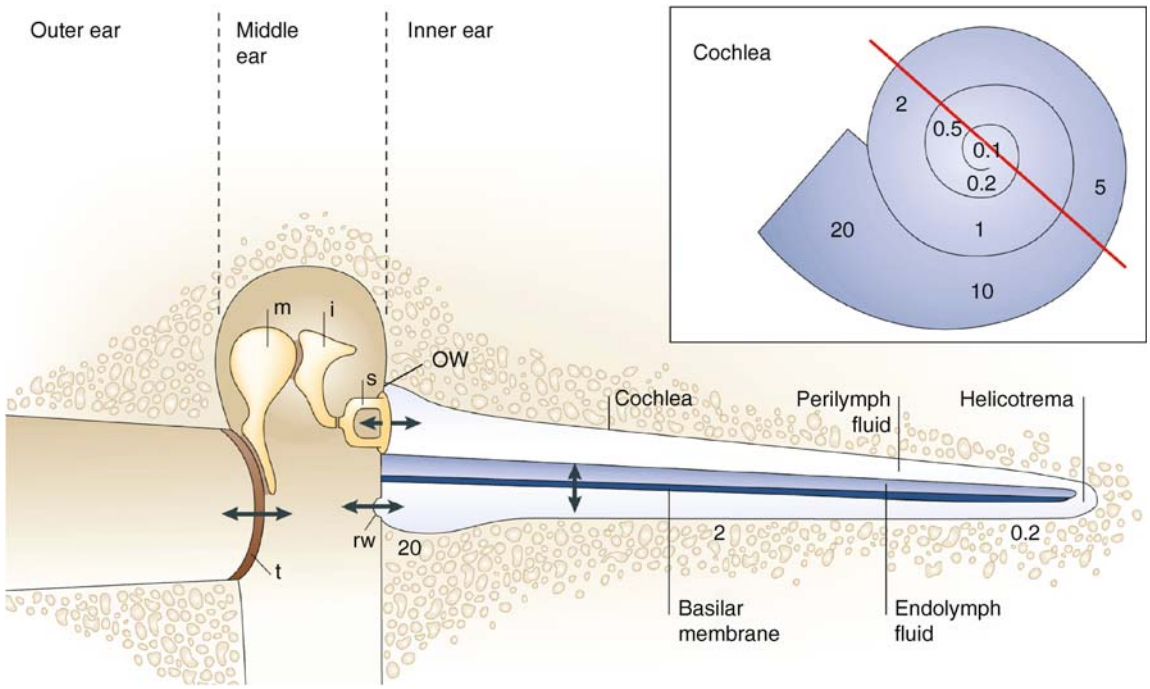
The ►cochlea is the hearing organ of mammals, located in the inner ear. It contains the ►organ of Corti, where ►hair cells convert ►sound-stimulated vibrations into electrical signals.

Characteristics

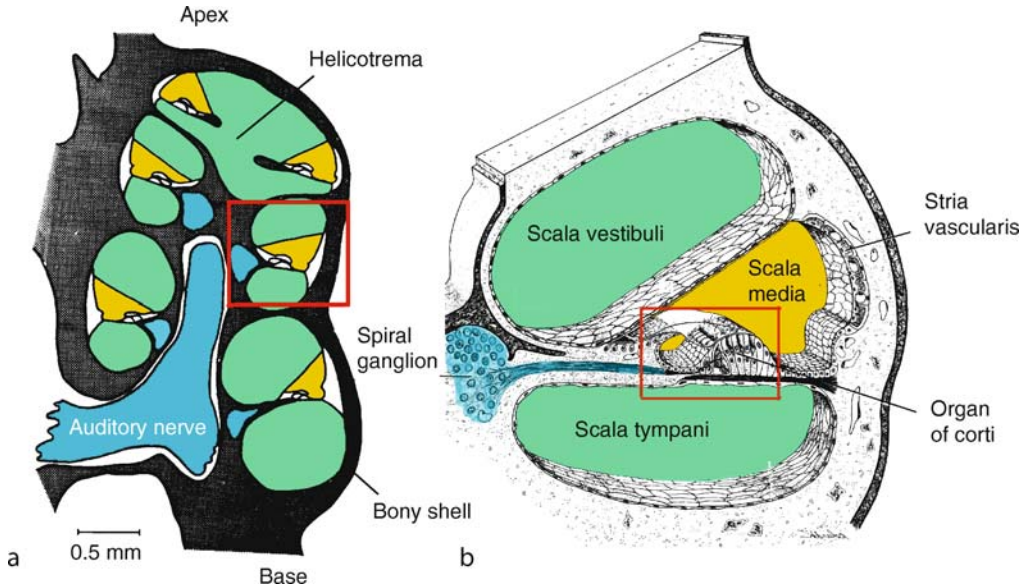
Anatomy of the Mammalian Ear

All vertebrate animals possess hearing organs which convert sounds (see ►Acoustics) into neural signals for transmission to the auditory centers of the ►brain. The cochlea is the hearing organ of humans and other mammals (Figs. 1 and 2). (The hearing organs of non-mammalian vertebrates differ substantially from the cochlea; see ►Avian Auditory System). Sounds stimulate the cochlea via vibrations of the tympanic membrane (eardrum) and the three middle-ear ossicles (malleus, incus and stapes) (Fig. 1).

Enclosed within the bony shell of the cochlea are three stacked fluid-filled membranous tubes, the organ of Corti (the organ of hearing proper), the spiral ganglion (containing the somata of ►auditory-nerve afferents) and various accessory structures, which jointly coil around a central axis (Figs. 1 and 2). The outer tubes, scala vestibuli and scala tympani, contain perilymph, which resembles other extracellular fluids, such as ►cerebro-spinal fluid, in that they contain a relatively a high concentration of sodium ions and a low concentration of potassium ions. Scala vestibuli and scala tympani communicate with each other via the helicotrema at the apex of the cochlea (Figs. 1 and 2a). The inner tube, scala media, contains ►endolymph, with ionic composition (high potassium concentration and low sodium concentration) unusual for an extracellular fluid, which sustains a



Cochlea. Figure 1 A cartoon of the mammalian ear. *Inset*. The cochlea coils around a central axis and resembles a land snail (hence its name). *Red line* indicates the plane of section for Fig. 2a. *Main*. the cochlea is shown uncoiled, in longitudinal section. m: malleus; i: incus; s: stapes; t: tympanic membrane; ow: oval window; rw: round window. The basilar membrane performs a spatial frequency analysis, with high-frequency sounds (e.g., 20 ►kHz or ►kHz: "20") causing largest vibrations at the cochlear base, near the round window, and low-frequency sounds (e.g., 0.2 ►kHz: "0.2") eliciting peak vibrations at the apex, near the helicotrema. Modified after Fig. 1 of [1], by permission of Macmillan Publishers Ltd.: Nature Reviews Neuroscience, copyright 2006.



Cochlea. Figure 2 *The cochlea*. (a) Cross section along its central axis (see *red line* in inset of Fig. 1). *Green*: perilymph fluid in scala vestibuli and scala tympani. *Yellow*: endolymph in scala media. *Blue*: auditory nerve and spiral ganglion. *Red* rectangle encloses an area comparable to Fig. 2b. (b) Cross section through a single turn of cochlear spiral. Red rectangle encloses an area comparable to Fig. 3a. Figure 2a modified after Fig. 13a of [2], by permission of Wiley-VCH, copyright 1991. Figure 2b modified after Fig. 35–10 of [3], by permission of Chapman & Hall, copyright 1994.

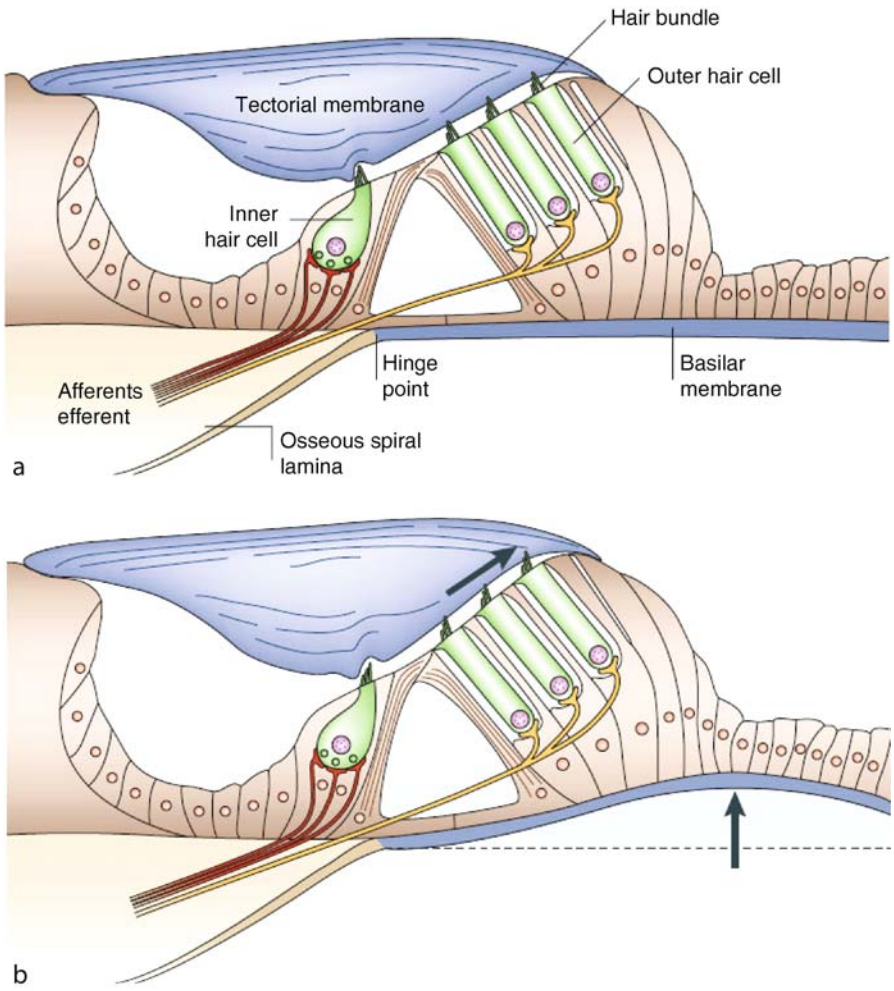
large electrical potential (+80 mV relative to perilymph). The lateral or peripheral wall of the scala media contains the stria vascularis (Fig. 2b), a richly vascularized tissue responsible for the ionic composition and electrical potential of endolymph.

The organ of Corti, which is attached to the ►basilar membrane, contains hair cells, the transducers that convert vibrations into electrical signals, and the peripheral terminals of the afferent and efferent ►neurons (Figs. 2b and 3a). Arranged longitudinally along the cochlea there are a single row of ►inner hair cells and three rows of ►outer hair cells. Bundles of "hairs" (rigid microvilli or ►stereocilia) protrude from the apical poles of the hair cells into scala media, where they are bathed by endolymph. Overlying the organ of Corti is the tectorial membrane, which contacts the stereocilia of the outer (but not inner) hair cells.

The innervations of inner and outer hair cells differ greatly. The afferent innervation consists of neurons with somata located in the spiral ganglion which send their ►axons via the ►auditory nerve (Fig. 2) to the ►cochlear nucleus. The auditory nerve consists largely of the axons of Type I afferent neurons, which amount to 95% of all afferent neurons and innervate inner hair cells exclusively. Thus, it is the inner hair cells that funnel most of cochlear signals into the brain. The efferents innervating the cochlea (Fig. 3) originate in neurons surrounding the superior olivary nuclei (see ►Efferent System and ►Superior Olivary Complex) and ►synapse with the outer hair cells and the Type-I afferent terminals.

The Basilar-Membrane Traveling Wave

The stapes transmits vibrations to scala vestibuli via the oval window at the base of the cochlea and the adjacent elastic round window, located over scala tympani, provides pressure relief (Fig. 1). The vibrations generate acoustic waves that propagate rapidly (within a few microseconds) throughout the cochlea. Those ("fast") acoustic waves, in turn, induce transverse vibrations of the basilar membrane and the organ of Corti which arise first near the stapes at the base of the cochlea and then travel relatively slowly (within a few milliseconds) toward the cochlear apex. As they propagate longitudinally along the cochlea, the "slow" ►basilar-membrane traveling waves grow larger, reach a peak and then they die out. At behavioral or neural ►thresholds (►sound pressure level of 0–20 ►dB), the peak of the basilar-membrane vibration is literally of atomic dimensions, about 1 nm [4]. The speed of the "slow" traveling waves vary as a function of distance: propagation is relatively fast at the basal end so that ►wavelengths are long; as waves proceed toward the apex, they slow down and wavelengths shorten. Because of travel time, basilar-membrane vibration phases increasingly lag stapes vibration as a function of distance from the stapes and, at any given site, as a function of stimulus frequency. Where traveling waves reach their peak



Cochlea. Figure 3 A cross section of the organ of Corti and the ►basilar and tectorial ►membranes. (a) Only the Type-I afferents, which innervate inner hair cells, and the efferents to the outer hair cells are illustrated. (b) When the basilar-membrane and the organ of Corti are displaced (*upward arrow*) toward the tectorial membrane, the stereocilia of outer hair cells are deflected radially, away from the inner hair cells. Reprinted by permission from Macmillan Publishers Ltd.: Nature Reviews Neuroscience, Fig. 2 of [1], copyright 2006.

depends on frequency: high-frequency waves peak near the stapes whereas very-low frequency waves travel all the way to the cochlear apex. In other words, the cochlea performs a mechanical Fourier analysis, mapping frequency into space so that each basilar-membrane site has a ►characteristic frequency.

Vulnerability and Nonlinearity of Basilar-Membrane Vibrations in the Living Cochlea

Basilar-membrane traveling waves can be demonstrated post-mortem in experimental animals, as well as human cadavers. This indicates that spatial frequency analysis in the cochlea is inherent in the physical (►passive) properties of the basilar membrane, which is narrow and stiff at the base of the cochlea and wide and relatively floppy at the cochlear apex. However, basilar membrane vibrations are crucially dependent on biological ("active") processes, so that they are much more sensitive and much more sharply frequency-tuned in living cochleae than post-mortem.

At the basal half of normal cochleae, basilar-membrane vibrations stimulated by tones with frequencies close to the characteristic frequency grow with stimulus intensity at compressive rates (i.e., <1 dB of vibration magnitude per ►decibel of stimulus magnitude), while response growth is linear at other frequencies. Hence, because the compressive ►nonlinearity is confined to frequencies near the characteristic frequency, ►frequency tuning varies with stimulus level: basilar-membrane responses are more sharply tuned, and exhibit more gain (vibration amplitude divided by stimulus level), for low-level than for high-level stimuli. Basilar-membrane vibrations in normal cochleae also exhibit other nonlinear phenomena, including two-tone suppression and harmonic and

intermodulation ►distortion, all of which are prominently reflected in the responses to sound of inner hair cells and auditory-nerve fibers, and in auditory perception (see ►Psychoacoustics). Following cochlear damage or death, basilar-membrane responses to tones with frequency far from the characteristic frequency remain unchanged while responses to tones with frequency near the characteristic frequency are drastically affected: they become linear, poorly frequency tuned, and less sensitive, their magnitude being reduced by as much as 60 dB.

In the basal half of the cochlea, the frequency selectivity and other properties of the responses of inner hair cells and auditory-nerve fibers derive more or less directly from the corresponding properties of basilar-membrane vibrations. The dominance of basilar-membrane vibrations in determining inner hair cell and neural responses is less clear for the apical half of the cochlea, where technical difficulties have made it difficult to measure vibrations in healthy cochleae. The few available data indicate that basilar-membrane frequency tuning is substantially less sharp at apical sites than at basal sites, in agreement with corresponding differences in frequency tuning in auditory-nerve fibers. The compressive nonlinearity is less salient at apical sites and, in contrast with basal cochlear sites, it is not confined to frequencies near the characteristic frequency, so that frequency tuning does not change as a function of stimulus level and is only minimally affected by cochlear trauma or death.

Hair Cell Receptor Potentials

When the basilar membrane and the organ of Corti vibrate, the stereocilia of outer hair cells, which are embedded in the tectorial membrane, are deflected radially (Fig. 3b). Organ of Corti displacements toward (or away from) scala vestibuli deflect the stereociliar bundle toward (or away from) the tallest stereocilia. How inner hair cell stereocilia are deflected is less clear. Since their stereocilia do not touch the tectorial membrane, it is presumed that they are deflected by streaming endolymph. When the stereocilia are in their normally erect position, a small ionic current flows from the scala media into the inner and outer hair cells. This current is modulated by changes in conductance associated with deflection of the stereociliar bundle: deflections toward and away from the tallest stereocilia cause conductance increases and decreases, respectively. The changes in conductance result from the ►gating of mechanically sensitive ion channels, non-specifically selective for cations, located near the tips of the stereocilia [5]. Gating is very fast, via direct mechanical interactions between the ►transduction channel and elastic filaments ("tip-links") which link adjacent stereocilia along the axis of maximum sensitivity. Upon bundle deflection, the tips of adjacent stereocilia are separated and the tip links pull open the transduction channels. When the transduction channels are opened, the electrical potential difference between endolymph and the cytoplasm of hair cells [+80 mV-(–60 mV) = 140 mV] pushes scala-media cations, principally potassium but also calcium (►Ca^{2+}), into the hair cells.

The modulation of the transduction current generates ►receptor potentials across the basolateral membrane of the hair cells; depolarization and hyperpolarization correspond, respectively, to increased and decreased current. Hair cell receptor potentials follow the deflections of their stereocilia monotonically and hence have frequency tuning roughly similar to that of basilar-membrane vibrations. However, hair cell transduction is nonlinear and currents and voltages are sigmoidal functions of stereocilia deflection. Furthermore, opposite but equal displacements of the hair bundle from the resting position generate unequal conductance changes, resulting in depolarization that is larger than hyperpolarization. As a consequence of this asymmetry, depolarizing DC ("direct current") responses are generated in addition to AC ("alternating current") responses. For high stimulus frequencies, the AC responses become smaller due to the shunting of the current by the parallel ►resistance and ►capacitance of the basolateral membrane of the hair cell, which jointly act as a ►low-pass filter. Nevertheless, inner hair cells can still signal the presence of high-frequency stimulation by means of their DC depolarization response, which grows bigger as the stimulus grows larger. Depolarization, in turn, causes release of excitatory ►neurotransmitter (►glutamate-like?) into the ►synaptic cleft of Type I afferent terminals (see Auditory Nerve). Since Type I neurons constitute the overwhelming majority of ►cochlear afferents and innervate solely inner hair cells, inner hair cells are viewed as the true transducers that funnel acoustic information toward the cochlear nucleus.

The Role of Outer Hair Cells in Cochlear Function

The outer hair cells probably play a negligible direct role in transmitting acoustic information to the brain but participate crucially in enhancing cochlear vibrations, increasing their sensitivity and frequency tuning. When moved by the basilar membrane, outer hair cells reciprocate by actively moving the basilar membrane. This positive feedback loop, which serves as a mechanical amplifier, was demonstrated by monitoring basilar-membrane responses to sound after systemic injection of furosemide, a diuretic which reversibly abolishes the endocochlear potential by shutting down metabolically driven ion pumps in the stria vascularis (Fig. 2b) and reduces hair cell transduction currents. The sensitivity, nonlinearity and frequency tuning of basilar-membrane responses to sound were drastically but reversibly reduced, an indication that cells of the

organ of Corti normally provide mechanical feedback to the basilar membrane [6]. The specific role of the outer hair cells was demonstrated by showing that stimulation of the medial efferent system, which innervates those cells, cause selective loss of sensitivity of basilar-membrane vibrations at the characteristic frequency [7].

The nature of the mechanical feedback from the outer hair cells is not certain. One candidate is somatic electromotility, the ability of outer hair cells to change length when subjected to fluctuating transmembrane voltages. In vitro, outer hair cells shorten when depolarized and lengthen when hyperpolarized. Somatic electromotility is not based on a muscle-like mechanism, since it does not directly require metabolic energy or calcium (Ca^{2+}). Rather, it reflects the collective deformations of millions of voltage-sensitive intramembranous prestin molecules. Prestin apparently plays a crucial role in cochlear function, since "knockout" mice lacking prestin have elevated hearing thresholds [8]. However, since the receptor potentials of outer hair cells are very small at high frequencies, it is difficult to envision how they can cause outer hair cell vibrations sufficiently large to influence basilar-membrane motion significantly.

Amplification mechanisms also exist in the hearing organs of non-mammalian tetrapod vertebrates, which broadcast ▶otoacoustic emissions (sounds emitted by the ear) much as mammals do [9] but which have neither prestin nor outer hair cells. In non-mammals, the very same stereocilia that mediate mechanical-to-electrical transduction also act as amplifiers of mechanical motion: for example, when mechanically stimulated, the stereocilia of frog sacculus hair cells generate more power than is present in the stimulus [5]. A similar mechanism may also exist in the outer hair cells of mammals, which in-vitro react to mechanical stimulation with active and nonlinear stereociliar motion [1].

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C

Cochlear Implants

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Definition

A cochlear implant (CI) is a prosthesis that electrically activates the auditory nerve in deaf patients to restore hearing sensations. CIs were originally developed in the 1960s and the early single-electrode devices restored only minimal hearing, with little or no ability to understand speech sounds. Modern, multichannel CIs restore hearing at a level that allows telephone conversation in most patients.

Characteristics

Quantitative Description

The CI (Fig. 1) consists of an internally implanted receiver/stimulator and an external signal processor.

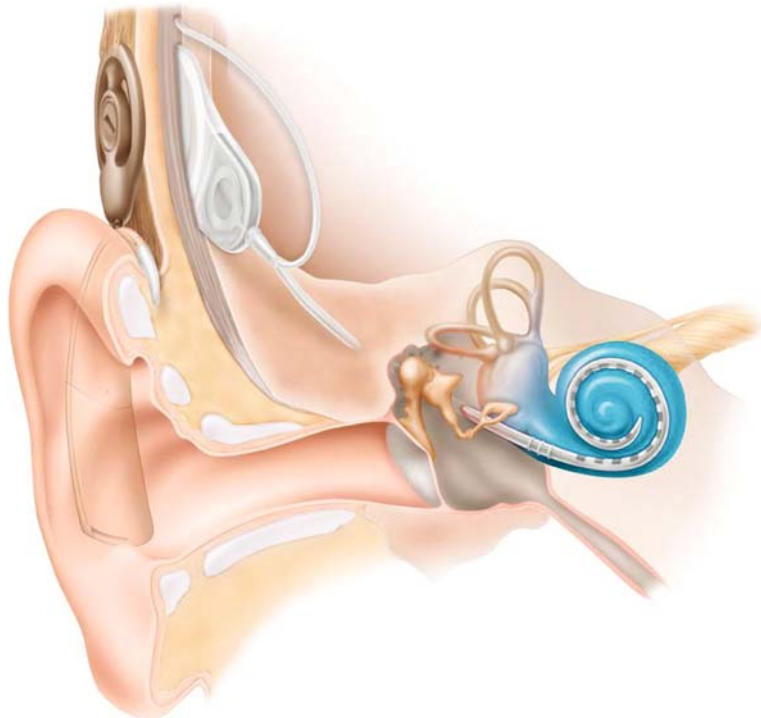
Modern multichannel CIs have between 16 and 22 electrodes in an array that is inserted through the round window into the scala tympani of the cochlea. Sound is received through a microphone and the acoustic signal is transformed to be appropriate for electrical stimulation. Typically, sound is split into 16–22 frequency bands and the energy in each band is compressed and applied to a different electrode implanted within the cochlea. Each electrode is stimulated with biphasic electrical pulses at rates between 250 and 5,000 pulses/s. Some CI devices allow presentation of analog electrical waveforms on each electrode.

Higher Level Structures

Although the CI activates neurons in the cochlea, the electrically driven neural activity then is processed by the auditory brainstem nuclei and auditory cortex. Areas of the cortex specialized for speech (e.g. Wernike's area, Broca's area) receive the abnormal pattern of neural activity. Pattern recognition processes and linguistic processes decode the distorted neural input into recognizable sounds and words.

Lower Level Components

The cochlea or inner ear is a fluid filled coiled structure that converts mechanical vibration of sound into nerve impulses to the brain. Most types of deafness result



Cochlear Implants. Figure 1 Schematic representation of a cochlear implant. The external portion of the device resembles a behind-the-ear hearing aid and consists of a microphone, sound processor and transmitter coil Auditory signals are received by the microphone, processed and transmitted across the skin to the implanted portion of the device. The implanted portion contains a hermetically sealed receiver/stimulator package, which receives and decodes the transmitted signal and the electrode array that is inserted into the scala tympani of the cochlea.

from the loss of sensory hair cells, which transduce the mechanical vibrations of sound into nerve impulses. The CI electrode array is placed in the scala tympani of the cochlea and is designed to activate the remaining neurons in a deaf cochlea. Modern CI devices contain 16–22 electrode contacts spaced along a silicone carrier. Electrode arrays are designed to be inserted 25–30 mm into the cochlea (normal cochlear length is 35 mm). Electrical signals are delivered to individual electrodes as either analog electrical waveforms or short biphasic current pulses. Auditory neurons are activated either on their peripheral processes (if they have survived the deafening pathology) or at the cell bodies of the spiral ganglion.

Structural Regulation

The normal cochlea is organized tonotopically; neurons near the base represent high-frequency information and neurons located at the apical end represent low-frequency information. The CI stimulating electrodes are arranged longitudinally along the silicone carrier to take advantage of this tonotopic organization. Electrodes at the base of the cochlea are stimulated to indicate high-frequency sounds and electrodes at the tip of the array (closer to the apex of the cochlea) are stimulated to indicate low frequency sounds. Temporal patterns of sound are represented as modulation in the amplitude of the stimulating electrical pulses.

Higher Level Processes

Since the pattern of neural activity has different temporal and spectral characteristics from that in a normally hearing ear, it is unclear how this abnormal pattern of neural information will be processed by specialized central processing mechanisms. Some complex auditory percepts, like musical pitch, require specific fine temporal information that is not represented by the CI [1]. These higher-level processes do not receive the peripheral information required for their function. Extracting signals in noisy listening environments also requires temporal and spectral fine structure that is not provided by the implant [2]. However, speech recognition and recognition of familiar environmental sounds relies on higher-order pattern recognition processing that is relatively insensitive to temporal and spectral fine structure [3]. Thus, most CI listeners can recognize speech at a level that allows conversational use of the telephone. When this level of auditory information is combined with visual cues from lip-reading, CI listeners can converse face-to-face at

near normal speaking rates. This pattern recognition is only obtained in adults who have been deafened after a period of normal hearing, whose central processing system has been trained by normal acoustic processing. Adults who are congenitally deafened are generally not able to recognize speech because their central brain mechanisms have not been trained by years of exposure to normal acoustic sound. Children who are implanted below the age of 2 years are able to recognize speech with the CI because their central processing mechanisms are still in a stage of biological plasticity and are able to effectively utilize the pattern of neural activity provided by the CI.

Lower Level Processes

Electrical stimulation of the auditory nerve produces abnormal patterns of nerve activation in terms of both the spectral and temporal dimensions. Temporally, electrical stimulation produces abnormally high phase locking, in which the nerve responds at precisely the same time within each stimulus cycle and all activated nerves fire synchronously [4]. In contrast, normal acoustic stimulation produces stochastic responses in proportion to the amplitude of the activating waveform, and each neuron is stochastically independent. Spatially (along the tonotopic dimension of the cochlea) the neurons are activated by the spreading electrical current field rather than by the mechanical traveling wave of the cochlea. Auditory nerve fibers are activated when there is a specific difference in the current at adjacent nodes of Ranvier. The current in the cochlea falls off as the inverse of the square of the distance between the electrode and neurons, modified by the geometry of the cochlea and cochlear fluids and the differences in impedance between fluid, soft tissue and bone. Measurement of the spread of activation from electrical stimulation [5] shows that the selectivity is poorer than with acoustic stimulation and that the selectivity depends on the electric field orientation and on the distance between the stimulating electrodes and neurons.

Perceptually, there is evidence [6] that speech recognition is correlated with the ability to detect amplitude modulation. CI listeners who do well on speech recognition tests can also detect 1–3% modulation, while listeners who are poor at speech recognition require more than 10% modulation for detection. CI speech recognition, while excellent under quiet listening conditions, is considerably poorer than normal hearing in the presence of competing talkers or competing wideband noise [2]. This reduction in performance appears to be due to the limited spectral resolution and to the limited access to temporal fine structure in CIs. Thus, it appears that the complex perceptual abilities of CI users are dependent on low-level peripheral processing. Signal processing methods that can improve the quality of the peripheral representation might result in improved speech recognition [7].

Process Regulation

Electric signals are processed in the CI to replicate as closely as possible the temporal and spatial pattern of neural activity in a normal acoustically driven cochlea. The CI can reproduce global aspects of the normal pattern of neural activation but cannot reproduce the fine temporal or spectral patterns present in a normal cochlea. The CI signal processor attempts to present electrical signals that will produce the most normal patterns of nerve activity.

Function

Modern multi-electrode implants were introduced in the 1970s and the level of performance has improved steadily so that in 2006 most deaf patients can recognize more than 95% of the words in simple sentences [8]. CIs are routinely implanted in deaf children under 1 year of age. Results show that children implanted under the age of 2 years are developing language at age-appropriate levels and rates [9,10]. Most implanted children are able to attend mainstream educational facilities with minimal special services.

Pathology

CIs are useful for any auditory pathology in which deafness results from the loss of hair cells. Most deafness is caused by the loss of hair cells and leaves the primary auditory neurons largely intact. Pathologies that cause the loss of primary auditory neurons are not suitable for a cochlear implant.

Therapy

Cochlear implants are a proven prosthetic therapy for most types of deafness. CIs allow post-lingually deafened adults and congenitally deaf children to recognize speech at a level that allows fluent conversation, even over the phone.

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Cochlear Nerve

Synonyms

N. cochlearis; Cochlear nerve

Definition

First section of the auditory tract. Is part of vestibulocochlear nerve (VIII) and goes from the spiral ganglion (first neuron of the auditory tract) to the cochlear nuclei. The fibers are organized in strict tonotopic fashion (ace. to tone frequencies).

►Auditory Nerve
►Nerves

Cochlear Nucleus

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Synonyms

Cochlear nuclear complex

Definition

The cochlear nuclear complex (CNC) is the first relay center in the auditory brain. From here the signals of the cochlear nerve diverges into a number of parallel ascending tracts, each with its own particular course and destination, as well as conduction velocities, properties and relays.

Characteristics

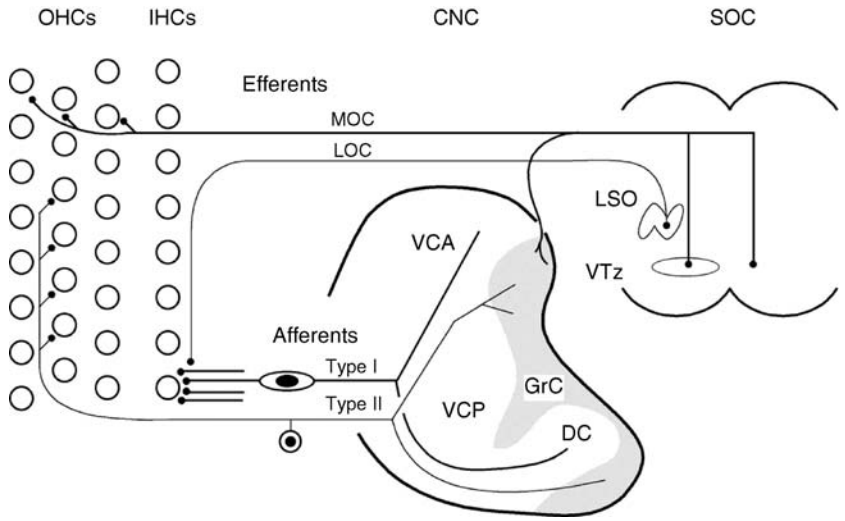
Introduction

The cochlear nucleus (CN) is the site of termination of all auditory nerve (AN) fibers and is thus the first relay center of the ascending auditory pathway [1]. The axons of CN projection neurons use three primary pathways to reach higher auditory structures, the dorsal, intermediate and ventral ►acoustic striae (DAS, IAS, and VAS respectively; the VAS is also referred to as the trapezoid body). The CN receives descending projections from the auditory brainstem, midbrain and cortex as well as other non-auditory brain structures [1]. There are some interspecies variations in the location and spatial orientation of the CN, most probably due to differences in the shape of the brainstem [2], but across species the CN consists of a ►ventral cochlear nucleus (VCN,). and a ►dorsal cochlear nucleus (DCN) The former is subdivided by the cochlear nerve root into an ►anteroventral (AVCN) and a ►posteroventral (PVCN) nucleus. As it enters the CN, the typical AN fiber bifurcates into an ascending branch, which supplies the AVCN, and a descending branch, which supplies the PVCN and DCN [3]. Fibers from the apical, low frequency part of the cochlea divide ventrally and terminate within laminar fields in the ventrolateral part of each division of the CN, while those from more basal, high frequency parts of the cochlea divide progressively more dorsally and medially and supply laminar fields in the dorsal parts of the CN subdivisions [2] The anatomical distribution of the primary fibers forms the basis for the physiologically demonstrated ►tonotopic organization of the three subnuclei [2].

Primary Afferents

There are two types of AN fibers: Myelinated type I axons carrying auditory information from cochlear inner ►hair cells and unmyelinated type II axons carrying unknown information from outer hair cells (Figs. 1 and 2).

All recordings from AN fibers have been from type I axons which can show high, medium or low spontaneous activity, a physiological feature that is correlated with the location of the synapse of the fiber on the inner hair cell. In response to pure tones at their characteristic frequency (CF, the sound frequency at which a cell responds with the lowest threshold) high CF type I axons display a primary-like (onset response followed by a gradual reduction in driven rate) ►peristimulus time histogram (PSTH) whose threshold is dependent on the



Cochlear Nucleus. Figure 1 Diagrammatic representation (modified from Brown et al. 1988, [4]) of the efferent and afferent innervation of the cochlea illustrating the hair cells of the cochlea (*left*), the cochlear nucleur complex (*middle*) and the superior olivary complex (*right*). The three rows of outer hair cells receive medial olivocochlear efferent inputs from axons of neurons in the medial aspect of the superior olivary complex. The outer hair cell output to the cochlear nucleus is via thin unmyelinated type II auditory nerve fibers that branch and innervate the granule cell region. The single row of inner hair cells receives lateral olivocochlear efferent inputs from axons of neurons in the lateral aspect of the superior olivary complex. The inner hair cell output to the cochlear nucleus is via thick myelinated type I auditory nerve fibers that branch and innervate the core region. See text for details. Abbreviations: *CNC*, cochlear nucleus complex; *DC*, dorsal cochlear nucleus; *GrC*, granule cell area; *IHCs*, inner hair cells; *LOC*, lateral olivocochlear fibers; *LSO*, lateral superior olive; *MOC*, medial olivocochlear fibers; *OHCs*, outer hair cells; *SOC*, superior olivary complex; *VCA*, anteroventral cochlear nucleus; *VCP*, posteroventral cochlear nucleus; *VTz*, ventral nucleus of the trapezoid body.

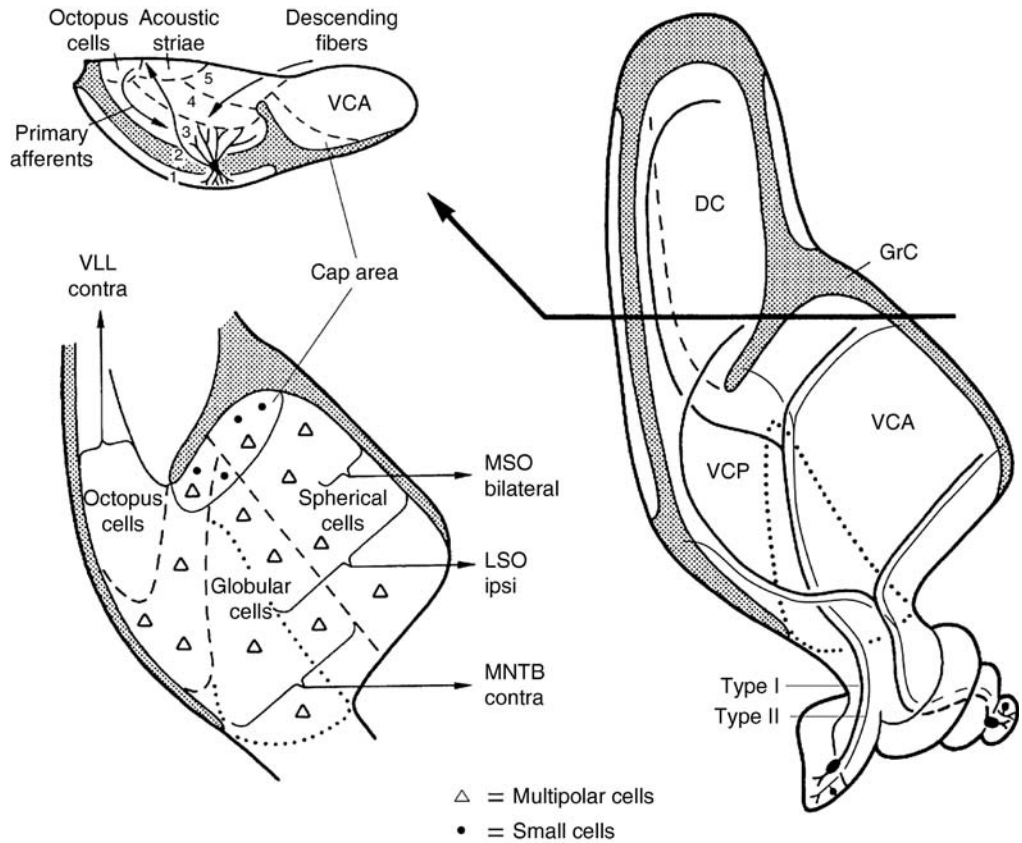
AN spontaneous rate. Low CF fibers show phase locking (spiking at a specific phase of each stimulus cycle). Both fiber types possess similar bifurcation patterns as they enter the CN, but the mode and total terminal area of termination differ. Type I fibers supply all parts of the CN except the periphery and granule cell areas (Fig. 1) [3] and produce large, axosomatic endings called "bulbs of Held" as well as small boutons (Fig. 3) [2,3].

These bulbs of Held arise mainly from the ascending branches, while the small boutons arise from loosely ramifying collaterals of both ascending and descending branches [2,3]. The type II fibers do not form bulb of Held endings and innervate areas rich in granule cells and appear to supply the marginal shell of the VCN as well [2,3].

Ventral Cochlear Nucleus

The VCN contains five main cell types (Fig. 2): spherical bushy, globular bushy, ►octopus, multipolar and small cells [3], that may be collected into two groups according to their dendritic architecture, targets and distribution within the CN: (i) spherical, globular and octopus and (ii) multipolar and small. The spherical ►bushy cells are found rostrally in the AVCN, the globular bushy cells lie centrally on both sides of the nerve root in the caudal AVCN and the rostral PVCN, while the ►octopus cells are found caudally in the PVCN. Multipolar and small cells are present throughout the VCN. The small cells are most abundant around the peripheral margins of the nucleus deep to the superficial granule cell layer. A distinct collection of small cells located dorsolaterally in a superficial location forms the small cell cap of the VCN (Fig. 2) [3]. Each cell type defined anatomically has several features which allow them to convert their auditory nerve input into a unique response characteristic of that cell type. These features include (i) the location, size and timing of activation of these AN synapses on the cell, (ii) the relationship of these AN synapses to other inputs from other sources and (iii) the unique features of the postsynaptic receptors and their currents and what ion channels these receptor currents activate. A discussion of the unique features of each CN cell type is beyond the scope of this chapter but several reviews are available (e.g. [6]).

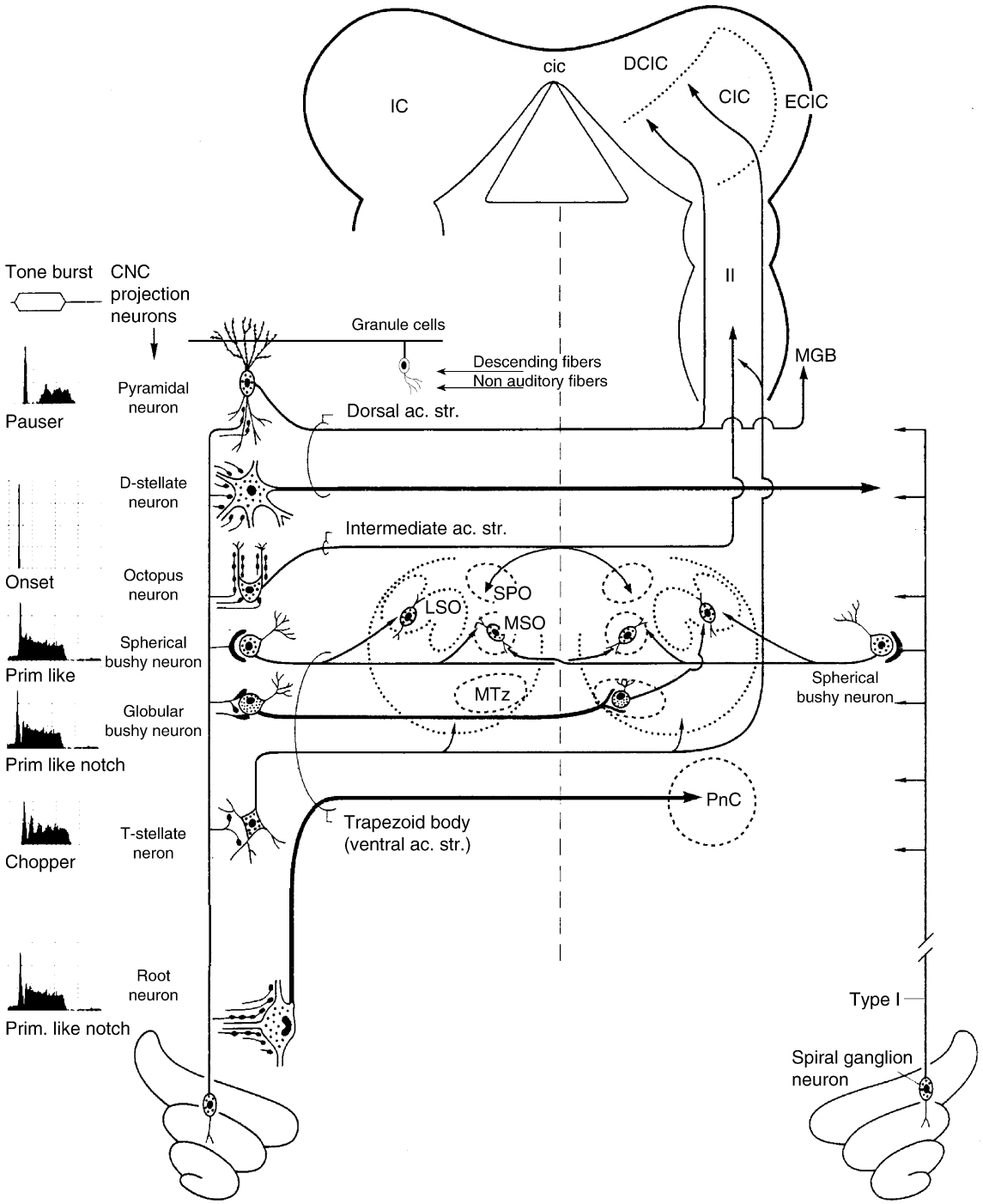
Each bushy (globular or spherical) cell receives a small number of bulbs of Held, has non-tapering dendrites ending in numerous small branches and an axon that projects into the trapezoid body (Fig. 3). Spherical- and globular bushy cells differ with regard



Cochlear Nucleus. Figure 2 Diagrammatic representation (modified from Osen, 1988, see [4]) of the major cell types in the cochlear nucleus. **Right**: Sagittal view of the major subdivisions of the cochlear nucleus and its innervation pattern by auditory nerve fibers. Both type I and II fibers from the high frequency base and low frequency apex of the cochlea are represented illustrating how the tonotopic map is formed in the cochlear nucleus by the type I fibers. Type II fibers project to the granule cell area in a non tonotopic fashion. ***Lower left:*** Bottom portion of the same illustration showing the location of the major cell types in the ventral cochlear nucleus and the major termination sites of their axons (arrows). ***Upper left:*** Section through the dorsal cochlear nucleus, ventral cochlear nucleus and cap area (see arrow and line through figure on right for location) illustrating the layers of the dorsal cochlear nucleus (1–5), how the auditory nerve fibers enter (curved line with arrow) and a ►fusiform cell in the fusiform cell layer whose axon is entering the acoustic stria. See text for details. Abbreviations: *DC*, dorsal cochlear nucleus; *GrC*, granule cell area; *VCA*, posteroventral cochlear nucleus; *VCP*, posteroventral cochlear nucleus.

to the number and relative length of the stem dendrites, the morphology of the terminal bush and their axonal projections to the superior olive. Spherical bushy cells with CFs below 10 kHz send their primary axonal projection bilaterally to the medial superior olive and to the ipsilateral lateral superior olive (Fig. 3) but there may be a set of spherical bushy cells with higher CFs that only project to the ipsilateral LSO. The primary axonal projection of the globular bushy cell is to the contralateral medial nucleus of the trapezoid body (Fig. 3). Spherical bushy cells which have high CFs possess primary-like PSTH responses to pure tone stimulation (Fig. 3), similar to those of the AN fibers [7]. Globular bushy cells with high CFs usually respond with a primarylike-with-notch (abrupt onset peak followed by a brief pause and then a resumption of sustained activity) PSTH while low CF units show phase locking that is better than their AN input. Many of the unique properties of the bushy cell membrane and its AN input make this cell capable of transmitting precise temporal information necessary for both high and low frequency sound localization [7].

The octopus cells receive small boutons from collaterals of a number of AN fibers on their dendrites (Fig. 3). Their main axonal projection is via the IAS to the superior paraolivary nucleus on both sides and to the contralateral ventral complex of the lateral lemniscus where some fibers terminate in large calyx-like synaptic endings (Fig. 3). They respond at CF with a single onset spike to a tone burst [7] (Fig. 3) and can respond to



Cochlear Nucleus. Figure 3 Diagrammatic representation (modified from Moore and Osen, 1979, see [4]) of the major projection neurons in the cochlear nucleus (CN), their innervation pattern by type I auditory nerve fibers, their responses to tones and the major termination sites of their axons outside the cochlear nucleus Peristimulus time histograms (PSTs) on the left represent the typical responses of the named cell type to short tone bursts. Cell drawings show representative auditory nerve fiber input size and location on the major CN projection cells. Axonal projections of these cells illustrate their pathway out of the CN and their major termination sites in nuclei outside the CN. Only the spherical bushy cell is represented on the right side to illustrate one of the known convergent circuits from the two cochlear nuclei. See text for details. Abbreviations: *cic*, commisure of the inferior colliculus; *CIC*, central nucleus of the inferior colliculus; *DCIC*, dorsal cortex of the inferior colliculus; *ECIC*, external cortex of the inferior colliculus; *LSO*, lateral superior olive; *II*, lateral lemniscus; *MSO*, medial superior olive; *MTz*, medial nucleus of the trapezoid body, *PnC*, pontine reticular nucleus.

click stimuli at rates up to 800/s with remarkable precision. The unique membrane properties of these cells, the distribution of their AN inputs and their unusual response features has led to suggestions that they encode the pitch period in their temporal firing patterns [8].

The multipolar cells receive ►primary afferents from many AN fibers by means of small boutons located mostly on their dendrites (Fig. 3). Two types of multipolar cells (type I and II) have been defined (e.g. [2]) but it is not yet clear how many subtypes may be represented within these two major classes. Corresponding cell types, given other names, have also been described in the mouse and rat. The type I correspond to the T-►stellate cells described in mice and planar neurons in rat [4]. They send what is presumed to be an excitatory projection via the trapezoid body to the periolivary region of the superior olive, the nuclei of the lateral lemniscus and the central nucleus of the IC [2] (Fig. 3). Some may also supply motoneurons of the middle ear muscles or send frequency specific collaterals to the DCN. In response to tone bursts, they show "chopper" responses (regular train of action potentials not related to stimulus frequency) and they are narrowly tuned in their frequency response. Choppers may be specialized for conveying frequency specific excitatory information about complex acoustic stimuli including speech. The type II multipolar cells correspond to the large D-stellate cells of the mouse [4] and radiate cells in rat [4]. Their axons exit the CN via the ►acoustic stria and project to the contralateral CN. For this reason they are referred to as commissural neurons [2] (Fig. 3). These multipolar type IIs are glycinergic [4] and function to provide wide band inhibition to several principal cell types in the CN bilaterally. Thus, they are the only known inhibitory projection neurons of the CN complex. They respond to pure tone stimulation with an "on-chop" pattern (2–3 onset peaks followed by little or no sustained activity) [5] and often respond over a very large frequency range (Fig. 3) A few published examples of type II multipolars with a slightly different form of PSTH (O_L, single onset peak followed by a pause and then a low level of sustained activity) have been reported but it is not yet clear where these cells project and whether they constitute a separate subpopulation. Nor is it clear what features of these various forms of stellate cells causes them to display different PSTH patterns (chopper, on-chop or O_L).

Very little information is available yet on the response features or the intrinsic membrane and synaptic features of those cells in the VCN classified as "small".

The CN of some rodents contains a population of large cells scattered in the cochlear nerve root (Fig. 3), between the main body of the VCN and the glial Schwann-cell border of the AN. These cochlear ►root neurons have dendrites oriented orthogonal to the AN fibers and receive small boutons from axon collaterals of AN fibers(Fig. 3). The cochlear root neurons possess an exceptionally thick axon (5–7 μm) that projects mainly to the contralateral reticular pontine nucleus. These cells respond with a short latency and, like globular bushy cells, show primary-like with notch PSTHs to tones (Fig. 3) [4]. It has been suggested that these root neurons participate in the acoustic startle reflex [4].

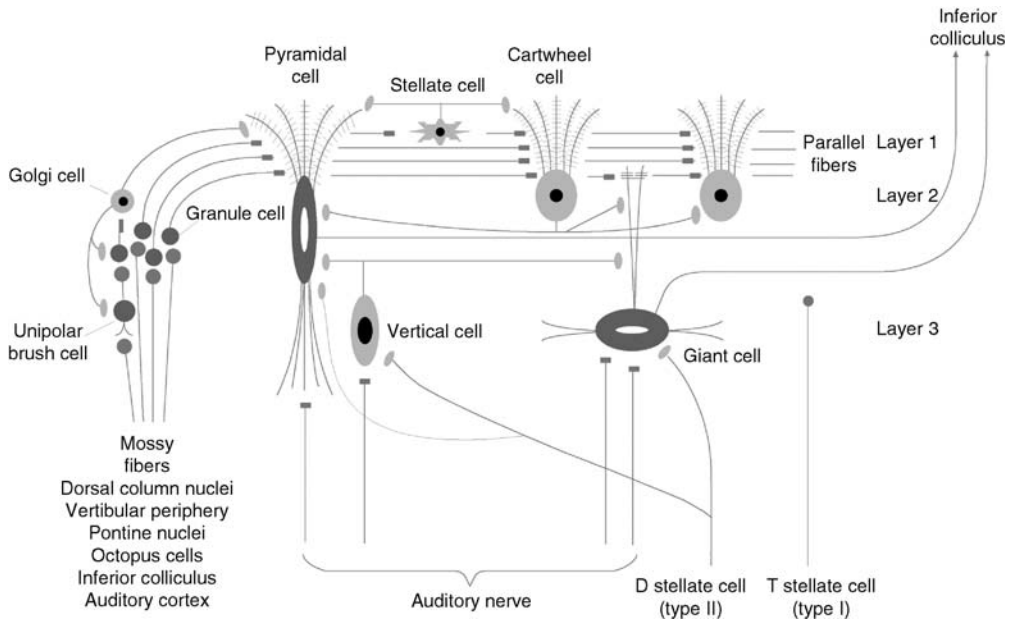
Dorsal Cochlear Nucleus

The ►DCN shows large interspecies variations and is virtually absent in some cetaceans. It varies from being markedly laminated in rodents and carnivores (Figs. 2, top left, and 4), where it resembles the cerebellar cortex, to being non-laminated in humans and some bat species (see e.g. [4,5]).

The three superficial layers of the DCN are related to the morphology of the principal ►fusiform cells (pyramidal). The spiny apical dendritic arbor of pyramidal cells occupies layer 1 together with granule cell axons and several other types of ►interneurons (see below). Pyramidal cell bodies define layer 2, and their aspinous basal dendritic arbors comprise layer 3. The pyramidal cells are the main ►projection neurons of the DCN, supplying fibers to the contralateral IC via the DAS (Fig. 3). In addition, some have a direct projection to the medial division of the medial geniculate body [4]. Pyramidal cell dendritic arbors are flattened across the long, frequency gradient axis of the DCN (see, e.g. [2,4]). The highest degree of flatness and mutually parallel orientation is found in the basal arbor, which is supplied by primary afferents in a strictly tonotopic manner. The deepest layer of the DCN contains two size categories of cells, the giant cells which project to the contralateral IC through the DAS and smaller glycinergic tuberuloventral interneurons. As in the ►VCN, each DCN cell type possesses unique anatomical, synaptic and intrinsic membrane features that allow it to convert auditory nerve input into a response pattern characteristic of that cell type.

Interneurons of the DCN may be divided into two systems, the ►granule cell system, related to the apical dendritic arbors and cell bodies of pyramidal cells and the tuverculoventral system, related to the basal dendritic arbors of the pyramidal cells (Fig. 4).

The granule cell system includes the excitatory granule cells and unipolar brush cells as well as three types of inhibitory cells: the GABAergic Golgi and stellate cells and the glycinergic cartwheel cells [5]. The granule cells receive direct excitatory input from many sources including the somatosensory system [1,2]. Inhibitory input from these same sources also reaches the granule cells indirectly via the Golgi cells. The granule cells contribute parallel fibers to layer 1 where



Cochlear Nucleus. Figure 4 Diagramatic representation (modified from Oertel and Young, 2004, see [5]) of the cell types and their connections in the superficial layers of the dorsal cochlear nucleus. See text for details.

they form asymmetric contacts en passant with the dendritic spines of both pyramidal cells and cartwheel cells and the smooth dendrites of the stellate cells. Such terminals show synaptic plasticity. The unipolar brush cells may represent a device for feedforward, excitation to links along the mossy fiber pathways. The stellate cells and cartwheel cells provide feed-forward inhibition to the pyramidal cells. Very little is known about the responses of cells in the granular cell system to auditory stimuli. Cartwheel cells show complex spikes (two or three action potentials riding on a depolarization) and weak responses to auditory stimuli that are difficult to classify.

The ▶tuberculoventral system reciprocally interconnects the DCN and VCN. It contains both frequency specific and diffuse projections [1,2]. The frequency specific projection from the DCN to the VCN originates from small interneurons, a subset of the glycinergic "vertical cells" (Fig. 4).

A separate set of vertical cells with only local collaterals contain both GABA and glycine, the relative amounts of which vary among species. They are located amongst the basal pyramidal cell dendrites in layer 3. The dendritic arbors of the vertical cells that project to the VCN are flattened and parallel to the pyramidal cell basal dendrites in the isofrequency planes. They receive primary afferents and project to the VCN via the tuberculoventral tract after giving off recurrent collaterals to the DCN, which terminate on pyramidal cells [2,3]. Thus, the vertical cells of the DCN provide tonotopically organized inhibition in both the DCN and VCN. Responses of positively identified vertical cells that do not project to the VCN (type II) are characterized by little or no spontaneous spiking, non-monotonic rate level functions, little or no response to noise and a tone-evoked PSTH that consists of an onset response followed by a gradual decrease in activity. The tonotopic, presumably excitatory projection from the VCN to the DCN is made up of the collaterals of type I multipolar or planar cells described above (see [4])]. The inhibitory projection from the VCN to DCN is composed of axons of the glycinergic commissural radiate or D-stellate cells described above. It has been speculated that off-CF or wideband inhibition from these cells might allow these cells to function as "spectral contrast detectors" [9]. Some small cells of the marginal shell surrounding the AVCN also project to the DCN. They receive ascending inputs from type II auditory nerve fibers and descending cholinergic inputs [4]. Thus, these cells emerge as very interesting players in the integration of neural activity in ascending and descending systems. Finally, yet another type of neuron referred to as adendric has been found to participate in the VCN to DCN projection (see [4]).

Pyramidal and giant cell excitatory responses are more strongly influenced by their inhibitory inputs than are those of other projection neurons in the CN, and have been classified as type III and IV [10]. Much of the inhibition is thought to arise from two cell types, the DCN vertical cells and the glycinergic type II stellate

cells in the VCN described above. The vertical cells provide inhibition over a narrow frequency range while the on-chop, type II stellate cells generate inhibition over a wide frequency range. This inhibition also presumably accounts for the response patterns of these cells to pure tones, which have been classified as "pauser" (Onset response followed by a pause then a resumption of firing, see Fig. 3) and "build-up" (a slow buildup of spike activity rather than an abrupt increase in firing). Behavioral studies in cats following surgical lesions of the dorsal and intermediate acoustic striae suggest that the DCN plays some role in directing attention to sound. The type IV units have been found to be sensitive to spectral notches created by the pinna, that may be important cues for localizing sounds. DCN projection neurons receive and respond not only to auditory information but to somatosensory inputs from muscle proprioceptors in and around the pinna as well [4]. Such evidence has led to speculation that the DCN output may be involved in coordinating pinna orientation with localization cues found in the different spectra of sounds located at different points in space (see [10]). In fact, bilateral lesions of the DAS in cats result in reduced accuracy in head orientation responses to broad-band sounds, particularly in elevation.

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Cocontraction

Definition

Simultaneous activation of muscles with opposite mechanical action on a joint (antagonists). Since the net torque acting on a joint is the algebraic sum of the torques generated by the individual muscles, torques with opposite signs cancel each other and the net torque may be zero. However, for a given net torque, the joint stiffness (the torque resisting an externally imposed joint displacement) increases with the level of cocontraction.

►Reaching Movements

Code, Coding

Definition

When information is stored, it has to be encoded. The nervous system stores information. Therefore, neurons must code information (see also ensemble code, grandmother neuron).

Coelacanth

Definition

Group of sarcopterygian fish once thought to be extinct but then found unexpectedly in an African fish market in 1938. Modern coelacanths are deep sea fin only rarely caught by fisherman and unable to survive in shallow waters.

►The Phylogeny and Evolution of Amniotes

Coenzyme Q10

Definition
A cofactor (a vitamin-like substance) upon which at least three mitochondrial enzymes (complexes I, II and III) depend for their function. The mitochondrial enzymes are essential for the production of energy in the cell.

Coeruleospinal Tract

Synonyms
Tractus caeruleospinalis

Definition
In the dorsal noradrenergic bundle of the locus coeruleus, fibers run in the direction of the spinal cord where they run in the lateral column and pass to all segments of the spinal cord, terminating in the posterior horn, in the anterior horn and in the intermediate substance. This portion of the coerulean efferents are globally called the coerulospinal tract.

►Mesencephalon

Cognition

Definition
Mental processes that includes – according to Neisser (Congitive Psychology, Englewood Cliffs, NJ: Prentice-Hall 1967) – transformation, reduction, elaboration, storage, recovery and usage of sensory information.

Cognition Enhancement

►Memory Improvement

Cognitive Aging

►Cognitive Impairment

Cognitive Behavior Therapy

Definition
A form of psychological intervention that focuses on changing maladaptive thoughts, beliefs and behaviors.

►Pain in Older Adults (Including Older Adults with Dementia)

Cognitive Decline

►Cognitive Impairment

Cognitive Development

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Synonyms
Intellectual development; Mental development; Development of thinking

Definition
Cognitive development refers to changes with age in human ontogeny in mental processes and abilities, that is, the development of higher mental processes such as problem solving, reasoning, conceptualizing, classifying, and planning, as well as more basic processes such as perception and language. Although modern developmental psychology studies psychological change over the entire lifespan, the field of childhood cognitive development is distinct from cognitive development in adulthood, in terms of theoretical issues and research paradigms. Only childhood cognitive development will be covered in this article.

Characteristics
Accounts of cognitive development in childhood address three major issues: (i) The initial (newborn) state, (ii) The description of "what" develops in children's thinking, and (iii) Accounts of how developmental change occurs. The field of childhood cognitive development was shaped by Jean Piaget (1896–1980) who viewed children's thinking as a source of insight into fundamental

epistemological issues (see [1], for an overview). Current theories of cognitive development generally subscribe to a view of human cognition as an information processing system and ask for similarities and differences between children's and adults' information processing. Most modern approaches can also be seen as alternatives to Piaget's theory, in the sense that they address major weaknesses of Piaget's theory and propose alternative solutions.

Piaget's Theory

In Piaget's view, infants begin life equipped with reflexes, perceptual abilities and basic learning mechanisms that allow them to actively construct their own knowledge. This constructive process starts at birth and is driven by the interplay of two complementary adaptive mechanisms, assimilation (the construal of external objects or events in terms of the child's present mental structures) and accommodation (the adaptation of existing mental structures in response to environmental pressure). Piaget viewed development as progression through an ordered sequence of stages which involves qualitative reorganization of the cognitive system. In the sensorimotor period (birth to 2 years) intelligence is bound to immediate perceptions and actions. Infants form sensorimotor representations of motor behaviors and construct fundamental concepts through their interactions with the environment. Piaget inferred cognitive immaturity from immature motor behaviors. For instance, he concluded from infants' immature search behaviors that they lack the concept of a "permanent" object that continues to exist independently of the infant's object directed actions. Towards the end of the sensorimotor period, with the onset of language, children acquire symbolic-representational thought. In the preoperational stage (age 2–7) children have the cognitive capability to represent past and future events, and to engage in symbolic activities. However, their cognition is limited by the inability to perform operations (reversible mental activities). Thus, they often focus on a single, perceptually salient aspect of an event, and fail to solve tasks in a logically consistent way. For instance, preschoolers are often misled by changes in appearance, such as the height of the level of liquid after pouring it from a wider into a taller, narrower glass. Their failure to mentally reverse the pouring operation results in a failure to "conserve" liquid quantity. Preschoolers' pre-logical thinking is also pre-causal and egocentric since preoperational children are limited in their ability to construct fundamental concepts that underlie our understanding of reality. In the concrete operational stage (age 7–11) children overcome these limitations and reason logically about concrete objects and events, based on fundamental concepts such as time, space, and causality. In the formal operational stage (age 11–15) young adolescents go beyond the limits of concrete operational reasoning in thinking hypothetically or theoretically about problem domains. They systematically test hypotheses and draw appropriate conclusions from their experiments according to the standards of scientific rationality.

Critical evaluations of Piaget's theory have focused on three major weaknesses [1]: (i) Empirical findings indicate that children's thinking at any given point in development is much less consistent than the stage model predicts. Thus, Piaget's elegant description of developmental change as a series of major cross-domain "structural" changes is not well supported by empirical evidence. (ii) Piaget greatly underestimated infants' and young children's cognitive capabilities. (iii) Piaget's theory is vague with respect to the mechanisms underlying developmental change. Since the 1970s the critical evaluation of Piaget's claims about young children's cognitive limitations has led developmentalists to adopt an "early competence" view of cognition in children: To mention just a few examples: Young preschoolers' causal reasoning is quite similar to adults' when task demands are kept simple, even toddlers master simple forms of visual perspective taking, rather than being fundamentally egocentric, and five-year-olds can integrate dimensional information, rather than focusing on just one dimension. Even more impressively, infants have been shown to be cognitively competent when tested with looking-time methods [2]. With the violation-of-expectation method it was shown that 3.5-month-olds are surprised when seeing a physically impossible event (a screen apparently passing through the space where a box was), thus indicating object permanence. Numerous studies have shown physical, numerical and social reasoning abilities in young infants which are inconsistent with Piaget's view of sensorimotor intelligence. Thus, Post-Piagetian research has led developmentalists to recognize similarities, rather than fundamental differences between children's and adults' thinking, and to emphasize continuity rather than discontinuity in cognitive development. Two major theoretical approaches have emerged as alternatives to Piaget's theory: Information-processing theories which focus on the development of domain-general capacities, such as processing speed and strategies, and theories of conceptual development which focus on the development of knowledge in foundational domains.

The Information-Processing Approach

Since the 1970s, information-processing accounts of cognitive development have productively used the metaphor of the child as a computational system. Like computers, humans suffer from limited information processing resources. Limitations may be due to hardware and/or software features, that is, the speed and efficiency with which basic processes are executed on

the one hand, and strategies and knowledge on the other hand. Information processing theorists attempt to specify in computational terms the cognitive processes underlying children's task performance, and the sources of developmental growth. This approach has led to a reinterpretation of some of the cognitive limitations described by Piaget. For instance, in Piaget's view, preschoolers' failure to draw correct transitive inferences ("Peter is taller than Max," "Max is taller than John." "Who is taller? Peter or John?") is due to the "structural" limitations of preoperational (pre-logical) thought. Training experiments showed, however, that preschool children can reliably draw transitive inferences when they are taught to memorize the premise information. Thus, developmental progress appears to arise from children's increasing ability to surmount processing limitations, rather than from a stage-like, qualitative change in logical reasoning abilities. The information processing approach has focused on problem solving and memory development [3]. Important determinants of memory development are speed of information processing, which increases greatly over childhood due to both biological maturation and experience, strategy development, the development of content knowledge and metamemory (memory-related knowledge and monitoring abilities). These cognitive processes interact in enhancing cognitive performance. While Neo-Piagetian information processing theories have retained the stage-model, describing children's thinking at each stage in information processing terms, and specifying developmental mechanisms, alternative theories focus on cognitive variability at each given point in development. Siegler [4] proposes an "overlapping-waves" model of strategy development, claiming that children possess more than one strategy for solving a given type of problem, and that strategic variability has an adaptive function throughout development. Other alternative information processing theories are ►connectionist theories, emphasizing parallel distributed information processing. Connectionist modeling has demonstrated that apparently discontinuous developmental changes may reflect gradual, incremental progress. While most information processing models have focused on a single aspect of cognitive functioning, ►dynamic systems theory [5] addresses the interrelations among perception, motor behavior, attention, language, and conceptual understanding. This approach has contributed to a revision of the interpretation of classical developmental phenomena, such as infant search errors which were attributed to a lack of conceptual understanding. The dynamic systems approach emphasizes the interplay between motor activities and attention in influencing success on such tasks, and has improved our understanding of how development progresses on a microgenetic level of analysis.

Conceptual Development

Both Piagetian and information processing approaches view development as a domain-general process of acquisition and refinement of cognitive abilities. Both approaches make minimal assumptions about the cognitive capabilities the infant is equipped with at birth (i.e. perceptual abilities, general learning mechanisms). In contrast, Post-Piagetian research on conceptual development emphasizes the domain-specificity of cognitive development, and makes assumptions about innate domain-specific knowledge and domain-specific learning mechanisms [6]. One reason to assume that domain-specific conceptual understanding underlies developmental change is that many claims about domain-general, across the board changes have been proven wrong. For example, Piaget attributed childhood animism (young children's tendency to attribute properties of living things to inanimate objects) to pre-causal thinking (a failure to understand mechanical causality, resulting in a tendency to explain all phenomena in terms of intentional causality). This interpretation cannot be correct, since more recent research found no deficits in preschoolers causal reasoning when tasks were chosen from domains that preschoolers were able to understand. An alternative explanation for childhood animism is a lack of conceptual understanding of biological phenomena (properties and functions shared by all living things) resulting in an overattribution of life to non-living things [7]. Knowledge acquisition in foundational domains (biology, physics, psychology) cannot be analyzed in terms of domain-general causal or logical reasoning, since each domain is characterized by specific core concepts and explanations. Thus, we explain psychological phenomena in terms of beliefs and desires, and physical phenomena in terms of gravity and inertia. Recent research on infant cognition indicates that young infants possess core knowledge in foundational domains: They expect physical objects to be solid and to move on continuous paths, they distinguish between living and non-living things, and they understand human action as goal-directed. Such findings support "core-knowledge" theories [8] which postulate innate domain specific systems of knowledge characterized by a set of core principles that define the entities covered by the domain and support reasoning about these entities. Such innate specialized learning abilities allow the infant to quickly acquire domain-specific knowledge of evolutionary importance. If core-knowledge is innate, what develops? There is evidence for both continuity and discontinuity in conceptual development [9]. Continuity can be seen as an enrichment of core principles. Discontinuity involves conceptual change. One model of conceptual change is theory change in the history of science [7].

An example of conceptual development in a domain of evolutionary importance is ►theory of mind development, that is, the ability to attribute mental states to

oneself and others (see [10], for an overview). Core concepts of our common-sense mentalistic explanations of human action are beliefs and desires. Children acquire a concept of belief (i.e. the ability to differentiate beliefs from reality) relatively late, around the age of four years. Desire-reasoning (in 2- and 3-year-olds) developmentally precedes belief reasoning, and reasoning about action goals can be demonstrated even in the second half of the first year of life. Children with autism suffer from a severe and specific delay in theory of mind development. Domain-specific theories of theory of mind development have recently received support from brain-imaging studies, indicating a specialized mindreading system in the human brain.

Conclusions

Cognitive development in childhood can be viewed as an interplay between domain-general changes in speed and efficiency of information processing, strategies, and metacognition, and domain-specific acquisition of conceptual knowledge. Research on infant cognition indicates that humans possess core knowledge in important domains early in life, possibly innately. Both enrichment of core principles and conceptual change contribute to cognitive development.

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Cognitive Dimension

Definition

The way an individual thinks about or processes information in response to a particular setting, process, characteristic, attitude, or sensation. A full description of a particular item would usually include the cognitive dimension of the item, along with its affective and behavioral dimensions (plus sometimes the sensory dimension).

Cognitive Elements in Animal Behavior

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Synonyms

Cognitive ethology; Complex behavior; Intelligent behavior; Flexible behavior; Adaptive behavior

Definition

Cognition can be seen as a "behavioral survival device" to solve problems in the individual's complex environment. According to Tomasello & Call's [1] ecological approach, cognitive processes "(i) are organized *flexibly*, with the individual organism making decisions among possible courses of action based on an assessment of the current situation in relation to its current goal, and (ii) involve some kind of mental *representation* that 'goes beyond the information' given to direct perception." Rather than simply coding outside information that is directly routed to motor output (e.g., as in reflexes), cognition involves all sorts of adaptable behaviors that evaluate information in the light of external and internal states to allow an individual to perform informed choices.

Over the last decades, it became evident that many complex behaviors cannot be understood without attributing mental, cognitive states to animals.

"Cognitive ethology" emerged as a new behavioral science to analyze high-level aspects of behavior, which, in turn, tremendously inspired brain research. Examples of cognitive phenomena that will be addressed in this essay are: (i) Categories & Concepts, (ii) Referential communication, (iii) Intentionality & Theory of Mind, and (iv) Conscious perception.

Characteristics

Higher Level Processes

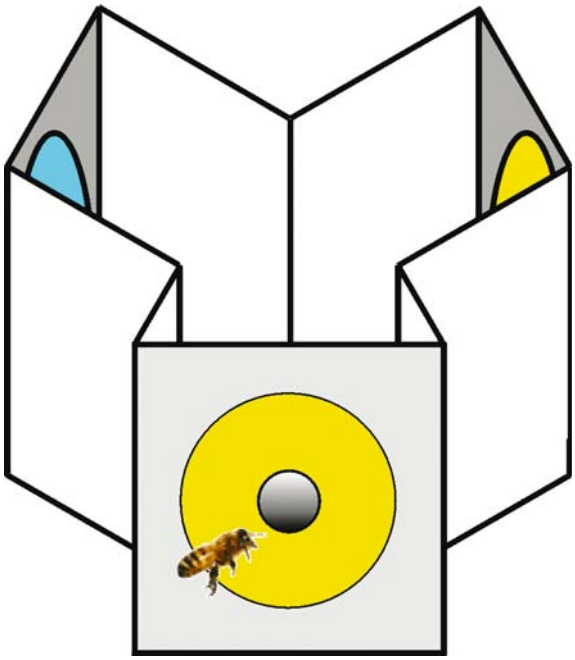
Categories & Concepts

Perceptual ►categorization refers to the recognition of different entities as members of the same group based on some internal representation. Strategies to achieve perceptual categorization are the memorization of individual stimuli, feature analysis, and the formation of prototypes. Categories provide useful grouping criteria across stimulus dimensions. For adaptive behavior, an individual must thus learn and memorize which objects can be regarded as being the "same," belonging to the same category, or being "different," belonging to another category. This involves the learning of abstract relations (e.g., more/less, same/different) to form categories, a process termed "►conceptualization" (or conceptual categorization, respectively).

Insects have long been viewed as simple reflex automata, not capable of complex behavioral flexibility. However, experiments in honeybees showed that at least some insects are endowed with complex visual learning and memory capacities, such as contextual learning, categorization and conceptualization. The classical behavioral protocol to test learning of relationships is the ►"delayed matching-to-sample" task. In such a task, animals are presented with a sample stimulus and temporally delayed with a set of test (or comparison) stimuli. One of the test stimuli matches the sample stimulus (in some feature dimension), and the animal's task is to always choose this correct match, despite the fact that the matching test stimulus is being changed regularly. Giurfa and co-workers [2] trained bees on a delayed matching-to-sample task in which they were presented with a changing sample stimulus (one of two different color disks, or one of two different black-and-white gratings) at the entrance of a maze (Fig. 1).

Once they entered the maze, the bees' task was to approach the test stimulus that was identical to the sample to receive a sucrose solution reward. For example, bees confronted with a yellow disk as sample stimulus were required to choose the yellow disk inside the maze and avoid the blue disk. Most importantly, bees that learned such a concept of "sameness" were able to apply it successfully in so-called ►"transfer tests," in transfer tests, subjects are confronted with novel stimuli they have never experienced before. In addition, to prevent subjects from learning a "correct" answer, choice behavior is not reinforced (i.e., the animals are randomly rewarded independent of their performance). The huge advantage of transfer trials is that they allow the investigation of how an animal applies rules learned in one situation to another, novel situation without having been conditioned by reward contingencies. Importantly, bees examined in transfer tests were able to apply the concept of "sameness" to new situations. For example, bees trained with texture stimuli and tested with color stimuli in transfer tests also solved the problem and chose the novel color corresponding to that of the colored disk at the maze entrance. Even more, transfer was not constrained to the visual domain (color versus pattern), but could also operate between different sensory domains, such as vision and olfaction. Bees that were trained to match odors (lemon and mango) were spontaneously able to match color in transfer tests.

Deriving the quantity of items is another, most abstract form of categorization. The ability to judge the number of items is highly adaptive; social animals such as primates make decisions to fight or flee by judging the relative number of friends versus foes. In foraging, choosing a larger alternative can contribute to survival. Not surprisingly, therefore, numerical competence



Cognitive Elements in Animal Behavior.
Figure 1 Delayed matching-to-sample test demonstrating categorization and conceptualization in bees. A graphical sketch of the experimental setup (y-maze) to test bees is shown. The sample is presented at the entrance of the maze (here: *yellow disk*). The bees should pass through the sample disk and choose the matching color (*yellow*) at the rear of the maze to receive sucrose solution. Adapted from [2].

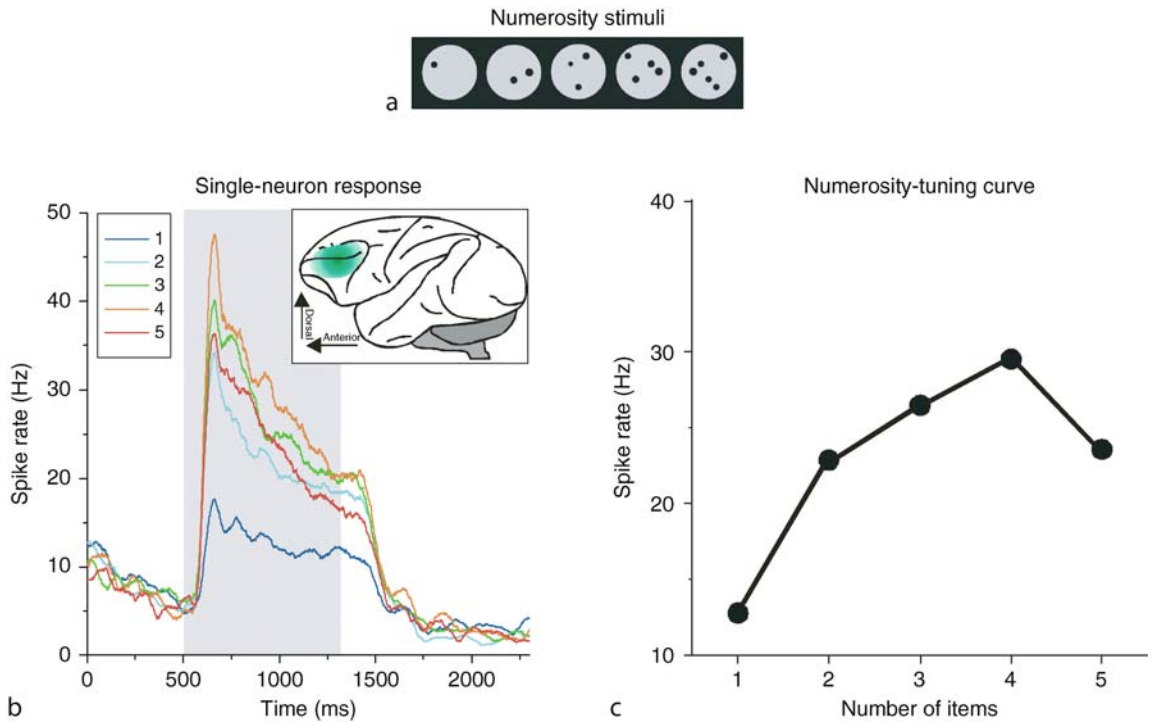
has been described in many species, most notably birds (corvids, parrots, pigeons) and mammals (rats, monkeys, apes). These animals show an approximate capacity to derive numerosity, they have a rudimentary understanding of *cardinal number* (estimating set size). Recently, a neural correlate for numerosity discrimination was described in the prefrontal cortex of monkeys performing a delayed matching-to-sample task based on the number of displayed items [3]. Single neurons were found to be tuned to different preferred numerosities (Fig. 2), thus forming a bank of overlapping quantity filters that can explain fundamental effects in numerical discrimination.

Beyond mere numerosity discrimination, an elegant study by Brannon & Terrace [4] demonstrated that rhesus macaques were even able to understand the ordinal relationship among numerosities; in other words, the monkeys understood that four was larger than three, but smaller than five. Numerical competence in animals is of special interest because it is thought to form an evolutionary precursor for verbal counting abilities in human adults.

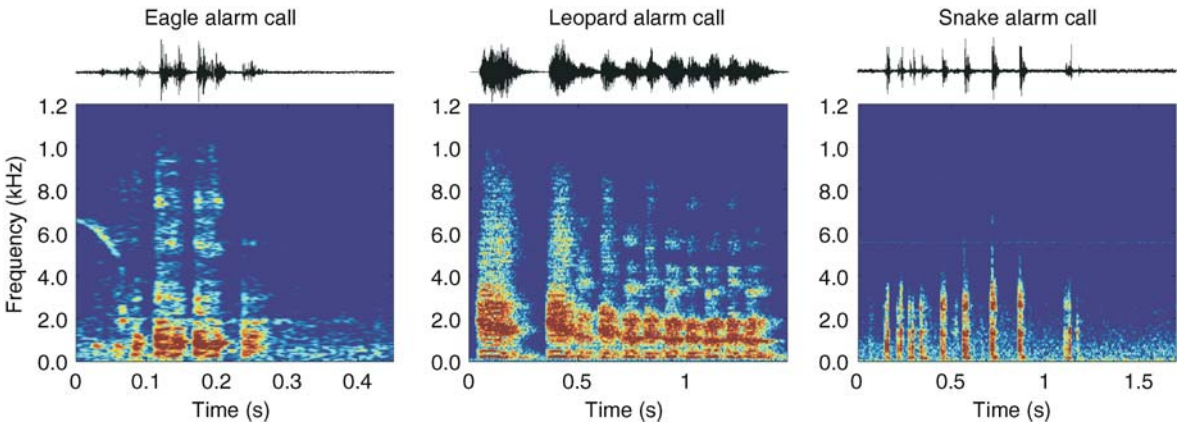
Referential Communication

Classification of stimuli can be based on sensory features. In social animals, however, such a simple classification scheme may fall short if there is a need to communicate information from one group member to another. Human speech is an impressive example of a communication system that is not primarily based on acoustic features, but rather on the meaning of a sound. Even though the words "enemy" and "foe" sound completely different in terms of their acoustic features, we know immediately that we are dealing with an opponent who may do us harm. Thus, humans categorize speech sound based on "referential" similarities, similarities in meaning (or semantics, respectively).

Vervet monkeys produce acoustically distinct alarm calls in response to potential predators (Fig. 3). The call types are specific for the type of predator (e.g., an



Cognitive Elements in Animal Behavior. Figure 2 Neural basis of numerical competence. (a) Rhesus monkeys were trained to discriminate the number of dots. While the monkeys performed the numerosity discrimination task, discharges from single neurons were recorded from the prefrontal cortex (see inset in B, showing a lateral view of a rhesus macaque brain with the prefrontal cortex shaded in green). (b) Spike density histogram illustrating the average response of a single neuron to numerosities one to five (see color code for line graphs). After 500 ms, the numerosity was displayed for 800 ms (time interval shaded in grey), which elicited vigorous discharges. The neurons, however, responded with different strengths to different numerosities. In (c), the same neuron's responses are averaged and plotted against the number of shown items. This very neuron formed a tuning curve and discharged maximally to numerosity "four", its preferred numerosity. Different neurons had different preferred numerosities. The neurons encoded abstract numerical information rather than visual parameters that may co-vary with an increase in the number of items (data not shown). Data modified from [3].



Cognitive Elements in Animal Behavior. Figure 3 Vervet monkey alarm calls. Vervet monkeys have three major call types to warn of predators (from left to right): "*eagle alarm call*", "*leopard alarm call*", and "*snake alarm call*". The calls are visualized as oscillograms (top panels, sound amplitude plotted against time) and spectrogams (*bottom panels*, sound frequency plotted against time, yellow to reddish color indicates high sound intensity). Note the different time scales.

"eagle alarm call" is only used when seeing flying birds of prey) and elicit specific and reasonable reactions (e.g., the monkeys climb up a tree when the "leopard alarm call" is heard). Experiments with playbacks (recorded alarm calls played through a speaker) demonstrated that recipients respond to the calls as they do to the actual predator in sight, which indicates that these calls may convey meaning [5]. Referential communication is also suggested through studies using the habituation-dishabituation protocol (animals habituate and stop responding to frequently repeated stimuli, but they dishabituate and become responsive again as soon as a novel stimulus is presented). It could be shown that habituation is not due to acoustic similarity of the alarm calls, but depends on the semantic context of the calls. For example, monkeys habituate if they hear an eagle alarm call followed by an original eagle call, but they do not habituate if they hear a leopard alarm call followed by an original eagle call. Therefore, these non-human primates appear to process alarm calls on a conceptual-semantic (i.e., referential) rather than a perceptual-acoustic level [6]. Referential signaling in monkeys, however, remains a controversial issue; it has been argued that vocalizations may simply elicit emotional (affective) responses in the recipient, which may then alter the recipient's behavior. Thus, alarm calls are often said to be *functionally* referential.

Intentionality and "Theory of Mind"

Do monkeys purposely warn their conspecifics of a potential prey, in other words, do animals intend to inform their group mates? Intentional states are characterized as being *about* things, like beliefs and desires, plans and wishes. From a philosophical point of view, different orders of intentionality are distinguished [7]: Organisms are said to have zero-order intentionality if they lack beliefs, desires or other intentional states at all, i.e., they show behavior as mere response to stimuli. First-order intentionality encompasses an agent having beliefs and desires about the world (e.g., a vervet monkey *wants* to warn a fellow monkey). Second-order intentionality would be evident if a sender *wanted* a receiver to *believe* something (in our example, a monkey giving a leopard warning call wants another monkey to believe that a leopard is approaching).

Neuroscientists studying the neural basis of expectation, planning, self-monitoring and the like would attribute desires, wishes and plans, and thus, first-order intentionality to "higher" animals. Whether animals have second-order intentionality, meaning that an animal is capable of having beliefs regarding another's beliefs, is a much more difficult question. Second-order intentionality, however, is a defining characteristic of what is called "theory of mind" (TOM). An animal has a TOM when it can form a representation of the beliefs, desires and capabilities of other animals, and so predict other animals' behavior and the probable consequences of their actions in an internal model. TOM may be a defining characteristic of adult human mental states that develops over the first years of childhood. Therefore, research on TOM has been done almost exclusively with non-human primates, particularly apes.

The strongest support for TOM in apes comes from recent experiments in which a dominant and a subordinate chimpanzee compete over food [8]. Normally, the dominant chimpanzee takes all the food in a competitive situation, and the subordinate misses out. However, when a subordinate can see a piece of

food that the dominant cannot see due to a physical barrier, the subordinate takes advantage of this situation by avoiding the food the dominant can see and instead pursuing the food the dominant cannot see. A subordinate also seems to know whether a dominant has just witnessed a human hiding food; the subordinate avoids the food the dominant has seen being hidden and instead pursues the food the dominant had not seen being hidden. These experiments indicate that chimpanzees can understand some psychological states in others.

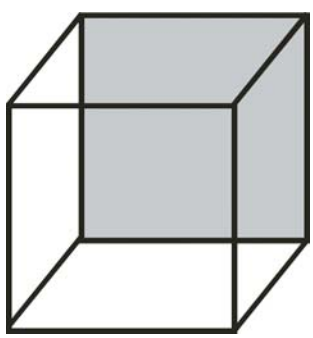
Conscious Perception

Consciousness can be divided into different aspects. Conscious perception, defined here as access to and evaluation of sensory representations to draw informed choices, has become the most rewarding line of neuroscience research to tackle the problem of consciousness. Bistable visual illusion phenomena offer a fascinating window into conscious processing. Bistable percepts result from the brain having to decide whether an image should be perceived in one or the other way, thus perception regularly switches between two different interpretations of a sensory input (Fig. 4).

Bistable percepts are also present in binocular rivalry phenomena, when two different images are projected onto the left and right eyes, respectively, but only one of them can be perceived in alternation. Logothetis and co-workers [9] exploited binocular rivalry by training monkeys to report whether they saw the left eye picture or the right eye picture at a given moment. While the monkeys reliably reported the perceptual switching between the two images, the researchers recorded the activity of single nerve cells in the visual brain of the behaving monkeys. Only neurons at advanced stages of the visual hierarchy, i.e., cells in inferior temporal cortex that are known to encode very complex visual stimuli (such as faces), responded vigorously when the monkey indicated to consciously perceive an image. These neurons remained silent without conscious experience by the monkey.

Another fascinating way to see consciousness at work is to study the ability to shift ►attention, thus being aware of features we attend to, while filtering out not attended aspects that do not reach conscious experience. Many animals are able to shift attention. For example, attention improves the ability of barn owls to localize a sound source; barn owls moved their head faster towards the direction of a sound source if they attended to this location. Electrophysiological recordings in behaving monkeys showed that neuronal responses to attended locations or stimulus features are enhanced, whereas those from unattended locations or features are suppressed. This influence of attention increases as one ascends the hierarchy of visual areas in primate cortex. At the highest processing levels, the neural representation of the visual world is dominated by the behavioral relevance of the information, rather than mirroring an accurate and complete description of it [10].

Conscious perception is an empirically addressable issue; other aspects of consciousness, however, may scarcely be accessible to objective investigations. The "hard problem" of consciousness relates to the question of how elemental personal feelings and impressions arise from neuronal discharges. These only-subjective experiences ("►qualia"), such as the taste of wine or the aching of a tooth, are only accessible via introspection. Whether other animals have "qualia", or even how this question may be addressed in an objective, scientific way, remains a fundamental philosophical question.



Cognitive Elements in Animal Behavior.
Figure 4 Necker cube. The drawing is perceived as a three-dimensional cube, but the perspective changes every few seconds: Note that the grey surface of the cube is sometimes seen as the rear panel, next time as the front panel. The Necker cube is a nice example of a bi-stabile percept, showing that conscious perception inevitably switches in certain ambiguous situations. Switching of conscious percepts is reflected in the responses of neurons in the primate visual cortex (see text).

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Cognitive Enhancers

Definition

Drugs that are proposed to enhance cognitive functions such as attention, learning and memory without affecting other physiologic functions in humans with cognitive deficits as well as in healthy subjects.

►Memory Improvement

Cognitive-enhancing Drugs

►Nootropic Drugs

Cognitive Ethology

►Cognitive Elements in Animal Behavior

Cognitive Functions

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Definition

Cognitive functions are concerned with mental processes and activities used in perceiving, remembering, problem solving and thinking. Cognitive functions are studied experimentally.

Introduction

This synopsis focuses on cognitive functions and how they are related to brain processes. Particular emphasis is given to knowledge based on behavioral research in cognitive psychology, which has established an inventory of well-defined tasks and sound experimental designs necessary for a thorough assessment of cognitive functions. However, the results based on behavioral research were not always conclusive regarding the underlying mechanisms. Either of two otherwise totally different psychological theories could sometimes equally well account for exactly the same pattern of behavioral results. Consequently, there was a need for an independent data source allowing for discrimination between competing theories. Only with the advent of new technologies do we now have such an independent database at hand. In particular, the study of neuronal activation enabled us to better understand the nature of the mechanisms that underlie a cognitive task. The combination of behavioral data paired with brain activation patterns can provide a strong support for a cognitive theory. Bridging the gap between cognitive performance and brain function is precisely the core idea of cognitive neuroscience. With the rise of this discipline a plurality of different methods has deeply enriched the study of cognitive functions. This synopsis will provide an overview of the main fields of research on cognitive functions, which is a rapidly growing field with many new insights yet to come.

The word cognition has its origin in the Latin word "cognoscere," which means "to become acquainted with, to get to know." Interestingly, the term cognition was not used until the nineteenth century and only then has it gotten more influential when it came to counter the claims raised by behaviorist psychology. Cognitive psychology acknowledged the existence of mental states and rejected introspection as a valid method of investigation. It has soon gotten evident that verbal reports would never suffice to tap into the underlying mechanisms. Moreover, unlike observable behavior cognitive operations are hidden and not directly accessible. Therefore, psychologists have begun to develop experimental methods, which help to tease apart the underlying mechanisms. The results from decades of behavioral research have provided an impressing wealth of knowledge. Nowadays, however, still many questions remain open for further investigation. What are the conditions for cognition to arise? When are brain processes associated with cognitive processes and when are they not? Are all brain processes involved in cognition? Or only some, and if so, which are the ones that qualify?

Sensory Processing and Perception

To date, a wealth of knowledge is known about ►visual perception (►vision), which is the most studied sensory

function. The essay on ►perception written by Dirk Kerzel will explain in detail how visual (and other sensory) processes operate. A distinction has often been made that characterizes early and late processes. Early processes involve elementary processes associated with the initial encoding of sensory information whereas late processes come into play when sensory information has been processed already and needs to be interpreted or categorized. Several cognitive scientists conceived an architecture of information processing steps, which is organized in different modules. Early processes involved in perception are separate from late processes, which involve more abstract and language-based thought processes. According to a strictly modular view early processes involved in the processing of perceptual information are completed before cognition comes into play; they are not cognitively penetrable [1]. Even though early processes appear more tied to the uptake of sensory input there is now growing evidence showing that activity in relatively early brain areas can be modulated by input form higher brain areas. Back projections from higher brain areas to early visual areas – the anatomical pre-requisite of ►top-down processes – have been demonstrated already, but empirical evidence that these projections are involved in cognitive functions is still relatively recent. For example, functional neuroimaging (e.g., ►fMRI) has revealed that activation in ►primary visual cortex is modulated by ►attention (►Visual attention). A study by Ress et al. [2] used a psychophysical target detection task (low contrast target on a uniform background) and demonstrated that the response in primary visual cortex was modified by the subject's attention, even when there was no sensory information present. The authors could also show that the activity in visual cortex was highly correlated with task performance. The greater the response the more likely the subjects were able to correctly detect the presence or absence of a pattern. Moreover, this research confirms earlier evidence based on recordings from single neurons showing that firing rates in monkey visual cortex are elevated by attention [3].

Attention and its Capacity

The study of basic sensory processes is important because cognitive operations can act on those data, thus providing us with a means to explore the nature of cognitive functions such as attention. The mechanisms of attention are elaborated more in detail in the essay written by Peter Klaver. Several aspects make this topic interesting in the context of cognitive functions, one of which is the selection of information. If a target object is defined by the presence of one salient feature it can be easily identified (e.g., a red ball on the lawn). In this case attention is automatically directed toward the object (this phenomenon is also known as *pop-out*). However, targets can differ by the conjunction of two features from the many irrelevant items present in a display. The search process is then time consuming and depends on the number of irrelevant items. Hence, visual attention can be guided via top-down processes to integrate object features or allocate spatial attention and it can be captured automatically via ►bottom-up processes. In fact, attention is not based on a single mechanism but is rather a composite of a plurality of numerous and partly distinct mechanisms. This is strongly supported by studies on the neuronal implementation of networks of attention. For example, disengaging visual attention from its previous location is associated with the ►posterior parietal lobe whereas the ►superior colliculus in the brain stem is involved in shifting attention to a new location.

Another important aspect of attention concerns its resources. The limits of attentional resources become evident when two tasks need to be coordinated at the same time. Compelling demonstrations have been given by studies on *inattentional blindness* [4], in which participants are engaged in a demanding task (e.g., counting events) while at the same time they fail to notice relatively obvious perceptual events (e.g., the appearance of a gorilla walking through a crowd of people [4]). In this context, it is noteworthy that research on attention is not only concerned with basic science. In fact, there are several applied implications such as the frequent use of video games and its impact on children's cognitive abilities. For example, there is evidence that video-game experts can have an enhanced capacity to process visual information [5]. Yet another topic covered by the essay written by Peter Klaver concerns the role attentional deficits play in cognitive disorders such as the ►ADHD – attention deficit/hyperactivity disorder.

How does the brain create a coherent and unique perception? When we search for an object the information processing in the brain is highly parallel. This means that different features of the same object are processed in different parts of the brain (for example, if the target is a green square). Nevertheless, we are able to combine different features such as color or shape to a coherent and unique conscious experience. This discussion is known as ►binding problem and Michael Herzog has written an overview about it. For example, it was suggested that the timing of different neural responses is in synchrony if they code for features of the same object. There are still open questions about the temporal patterns but future studies will probably clarify many issues of the binding problem and its relation to consciousness.

Memory and Mental Imagery

Only a few remarks will here be made about learning and memory, which are treated extensively in other contributions. The functions of memory are revealed

best by clinical cases from neuropsychology showing how some functions of memory can still be preserved while others are no longer available. For example, ►anterograde amnesia prevents the ability to consolidate new information in memory whereas previously stored information can still be retrieved. Interestingly, however, the ability to learn implicit tasks such as new motor skills remains intact. Memorizing implicit and explicit information draws on at least partly different neuronal mechanisms. Yet other dissociations concern the distinction between short-term and long-term memory or the distinction between episodic and semantic memory. Memory does not only serve the purpose to represent what happened in the past and, in fact, its nature is rather constructive and can lead to illusions or misattributions. For example, people can fail to correctly indicate the true source of their memories despite the fact that they strongly believe that what they remember did happen exactly the way they think. Yet another and often understudied type of memory is ►spatial memory, which is addressed in a separate essay written by Catherine Brandner.

Information stored in memory is also crucial when it comes to other cognitive functions such as mental imagery. Only the information provided by the senses can be stored in memory so that we can later retrieve it and use this information when we remember an event or imagine an object or a person. ►Visual memories are stored in temporal brain areas and research on mental imagery has in fact shown activation in those areas when people visualize objects or faces [6]. Some types of imagery require a high-resolution representation and neuroimaging studies revealed activation in early visual areas when subjects are engaged in such tasks. Specifically, this is the case when the task requires vivid and richly detailed images allowing for fine visual discriminations. Klein et al. [7] have shown that mental imagery of a bowtie-shaped figure with a checkerboard pattern activates voxels (volume elements) in primary visual cortex that overlapped widely with those voxels when people viewed the same stimulus. Depending on the orientation of the imagined stimulus the activation changed according to the corresponding perceptual condition. Moreover, converging evidence from studies based on other methods such as repetitive ►transcranial magnetic stimulation provided further evidence that early visual areas are in fact functionally involved in the process of visual mental imagery [8].

What is the functional relevance of early visual activation during visual mental imagery or attention? One interpretation suggests that mental imagery is in the service of perceptual anticipation [9]. Imagery has been described as "getting ready to see" and therefore (pre) activates those brain areas that are normally engaged in the processing of sensory input. This anticipatory function could facilitate the process of perception and finally lead to a faster or more reliable detection of a visual object.

It remains an open question as to what extent early visual activation during attention and mental imagery overlaps. Mental imagery and visual attention are still experienced differently and future research will better determine the differences between cognitive functions such as mental imagery, visual attention, and visual perception. However, this example shows to what extent different cognitive functions are nested and intertwined.

Reasoning

Yet another cognitive function is ►reasoning. Our brain enables us to reason and thus to go beyond what is actually given. Mental reasoning is the ability to infer conclusions based on previously established premises. Even though it is conceivable that reasoning as computational problem can be implemented in any type of hardware this assumption turned out to be wrong. Neuroimaging studies helped to constrain the wide range of possible mechanisms. For example, when people reason in the absence of any semantic context they use the visuospatial system in the right hemisphere involving parietal areas, ►precuneus, and the extrastriate (and sometimes striate) visual cortex (►Extrastriate visual cortex). Left temporal areas, however, come into play as soon as the reasoning task has a semantic content. Neuropsychological studies with patients have provided some knowledge already but it remained widely inconclusive as to what components of the reasoning process are in fact altered by the lesion. The essay on reasoning written by Markus Knauff is focusing specifically on reasoning and how different brain areas are drawn upon when people solve reasoning tasks.

Cognition and Motor Behavior

The involvement of the motor system (►Motor control) in understanding cognitive functions has long been underestimated and still today modern textbooks often miss a chapter on motor functions. The representation of an action is of particular interest because it links thoughts with observable actions. It is noteworthy that an action not only includes the planning and execution of a movement but also its recognition. Rizzolatti et al. [10] have discovered visuo-motor neurons in monkey's ►premotor cortex. These neurons respond to the execution of a particular movement and to the observation of the same movement. The discovery of the mirror neurons had far-reaching consequences on the understanding of the motor system and current research includes their involvement in the detection of others' intentions and how we interpret observed actions. The essay written by Laura Bamert and Fred Mast deals with yet other topics of ►action representation such

as motor imagery. Imagined actions share several commonalities with executed actions and there is growing evidence as to how execution can benefit from motor imagery training.

Cognitive Development

A promising area is the study of human brain development and how it is mapped to ►cognitive development. There is an increasing amount of evidence demonstrating that the gap between developmental psychology and neuroscience has in fact narrowed, and there are still more research interactions to be established between developmental psychologists and cognitive neuroscientists. Recent research in cognitive development has elucidated preschool children's abilities. Their competences are far more developed than previously assumed and include perspective taking, knowledge about emotions, and causal thinking. Beate Sodian has written an essay on cognitive development.

In the context of cognitive development, the role of brain plasticity has received considerable attention, for example the modification of synaptic strength that underlies changes in cognitive function. Moreover, there is an increasing amount of research showing how ►chronic stress can suppress neurogenesis and the remodeling of dendrites. This again elucidates the links between cognitive functions and brain processes. The recent years have strengthened the importance of cognitive factors that in combination with the environment regulate genes, ►hormones and ►transmitters.

Not only is it relevant to study cognitive processes at work but also the changes of performance over the entire span of life. Why and in particular how does cognitive performance decline? Future research in cognitive neuroscience will provide us with more profound knowledge about the aging brain, and how we can slow down the debilitating effects of aging. Ben Godde has written an essay on ►cognitive impairment, in which different theories on cognitive aging are discussed. The essay also addresses the neuronal mechanisms that underlie the aging processes and demonstrates that there is plenty of evidence showing reduced induction and maintenance of ►long-term potentiation (LTP) and reduced neurogenesis in ►hippocampus. Using neuroimaging, the aging brain can be studied in humans and the results revealed under- and overactivations. The latter is particularly interesting since it suggests a compensatory role for processing deficits in the sensory domain. Changes in the brain during aging are partly due to degenerative mechanisms but they can be influenced by the individual lifestyle. It has been found that cognitive performance and prefrontal and parietal activity is increased after a cardiovascular fitness program. Besides neuronal survival several other mechanisms are currently discussed and yet discovered that are responsible for the relation between cognitive functions and cardiovascular fitness.

Spatial Processing and Cognitive Functions

Spatial processing is involved in almost any cognitive function and knowing more about it helps to understand how basic cognitive functions operate such as attention, mental imagery, action control or perception [11]. When we open our eyes we are confronted with the visual perceptual world. The perceptual world is spatially organized, the figures are segregated from the ground, the objects are clearly defined by their contours and they appear to us in a defined spatial location (Vision). This is possible because the perceptual system establishes a spatial ►frame of reference allowing for correct evaluations of directions and coordinated actions. It has to be distinguished between an egocentric frame of reference, which is bound to an axis fixed to the observer's body, and an allocentric frame of reference, which is defined with respect to a spatial reference outside the observer's body such as visual landmarks in the environment. It is noteworthy that the allocentric frame of reference includes the gravitational force, which acts "invisibly" and is independent of the body. The two types of spatial coding differ also in terms of their neuronal underpinnings even though there is also substantial overlap of the brain areas involved [12]. The reference frame is explained thoroughly in the chapter on spatial memory written by Catherine Brandner.

►Spatial cognition is yet another topic related to spatial functions. This growing field is outlined in the essay written by Sarah Creem-Regehr. Depending on the actual task, the perceptual space has been classified as personal space (the space within reach), action space (the space in which we act and locomote), and vista space (the visual space we see beyond 30 m). Not only is the involvement of the spatial frame of reference absolutely evident in perception and orientation tasks but it also plays an important role in higher cognitive tasks such as mental imagery when there is no sensory information to be processed [13]. For example, we are able to mentally transform the egocentric frame of reference in order to make a spatial judgment from some other viewpoint outside of our own body. This other viewpoint could be fixed to another person. "Watch out, on your left side!" This is what we hear parents shout out aloud when they attend a soccer game and see their own child just going to be tackled by a defender from the other team. In this example, the parents need to take on the child's perspective and use it as reference for their spatial judgment. Spatial updating tasks have shown that mental transformations of one's own perspective are highly efficient and a performance advantage has been shown when compared to an

object-based strategy, in which they rotate mentally the visual representation of the surrounding environment.

Social Cognition

Even though it goes beyond the scope of this synopsis it should be noted that the study of cognitive functions is not independent of socially relevant information. Social psychology has been studying how people process social information and social cognition has gotten one of its most rapidly growing fields. For example, the mental ability to take on someone else's viewpoint has been discussed as a prerequisite of empathy. In fact, several other social phenomena involve cognitive processing such as attraction, competition, cooperation, and altruism. We are often not aware of how the underlying cognitive processes operate but they are powerful and can influence decision taking and behavior (e.g., in the case of stereotyping). In fact, several experimental tasks have been developed which require the participants to respond without having to verbalize their thoughts about other people or situations. Social cognitive neuroscience is one of the most recent advances in the field. This implies the study of social situations and relate those to brain activation.

Acknowledgments

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C

Cognitive Impairment

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Synonyms

Cognitive aging; Cognitive decline

Definition

Cognitive impairment describes the decline in cognitive functions like memory, ►selective attention, ►executive control, or conscious perception. This decline may be the consequence of lesions of the brain, or diseases like ►Alzheimer's disease (AD) or other forms of ►dementia, but often also accompanies normal aging. As compared to subjects suffering from dementia, people with so-called ►mild cognitive impairment (MCI) show only moderate loss of cognitive functioning, e.g., poor performance in memory tasks, but mostly no problems with activities of daily living. However, patients with MCI have increased risk of developing AD in their later life. Thus MCI can be regarded as intermediate stage between normal, non-pathological aging and dementia. During normal aging at least three different patterns of development can be distinguished. Whereas some cognitive functions decline continuously from very early in life, others remain stable or even improve. This essay will be restricted to processes of cognitive impairment during normal healthy aging.

Characteristics

Behavioral Changes

Cognitive impairment during aging is characterized by a high variability of developmental trajectories – between

individuals as well as within individuals for different cognitive functions. Whereas some cognitive functions decline continuously from very early in life (from 25–30 years of age), others remain stable or even improve. Cognitive functions that show increasing impairment with age are perception and processing accuracy, speed of processing and ►reaction times, the ►encoding of new memories into episodic memory and the ability to learn new things, the recall of information from long-term memory, the capacity of the ►working memory, executive control, selective attention, and inhibition of distracting information. These functions are attributed to the domain of so-called ►fluid intelligence or ►cognitive mechanics and are mostly biologically and genetically determined. According to the two-component theory of intelligence [1] they can be distinguished from functions belonging to the ►cognitive pragmatics or ►crystalline intelligence, e.g., verbal knowledge and comprehension, autobiographical memory, emotional processes, strategies of processing and learning, and learned skills like reading, writing, or occupational skills. These knowledge and wisdom based abilities remain not only stable but may be improved even at old age and are often able to compensate for decline in the cognitive pragmatics. As a consequence of these compensatory mechanisms, in normal aging cognitive impairment has only little impact for activities of daily living. Nevertheless, particularly under laboratory settings in which subjects have to perform two or more tasks simultaneously, differences in performance levels between young and old subjects increase with task complexity.

Theories of Cognitive Aging

There exist different theories about the causes of cognitive impairment during aging and the debate is still going on. General factors or *common cause* theories favor single biological factors to cause decline in most cognitive abilities. White matter integrity deficits or decreased signal-to-noise ratios might be responsible for a general slowing of cortical processing as indicated by increased reaction times for various cognitive tasks (*General slowing hypothesis*, [2]). Support for the common cause hypothesis comes from a close correlation between age-related changes in cognitive, sensory, and motor functions. Other explanations for this correlation might be that cognitive deficits cause sensory decline or that sensory deficits cause cognitive decline. However, no causal relationships in either direction between sensory and cognitive decline could be revealed. Thus *cross domain resource competition* together with decreasing resources available are a more likely alternative explanation.

The *frontal lobe hypothesis* states that neuronal decline in the frontal lobe, particularly the ►prefrontal cortex (PFC), has major impact for cognitive impairment since functions controlled by the PFC like executive control, selective attention, response inhibition, and working memory seem to be more affected by aging than functions that rely on activity in other cortical or even subcortical regions. One of the most recent theories argues that deficient dopaminergic ►neuromodulation due to a decline in the frontostriatal network is a promising correlate of cognitive impairment during aging [3]. It is argued that reduced signal-to-noise ratios due to a loss of ►dopamine support of the PFC may explain age effects in working memory, selective attention, inhibitory control, and other cognitive functions.

Recent evidence further revealed that common causes cannot easily explain all facets of cognitive impairment during aging and that age-effects vary considerably across tasks. These task-dependent age-effects indicate that one factor is not sufficient to explain cognitive impairment during normal aging but that both common and specific factors have to be regarded.

Evidence from Functional Neuroimaging

Functional neuroimaging reveals patterns of over- and underactivation in the aging cortex. As compared to young adults, older adults with difficulties in working memory and executive control often show reduced activity in the PFC [4]. Less activity in the ►hippocampal formation of the mediotemporal lobe (MTL) is related to impaired ►recognition memory and attentional orienting and novelty detection processes [5]. Underactivation has also been shown for sensory cortical networks like the occipitotemporal (ventral) visual pathway [5] and may be conceived as equivalent of reduced integrity of cortical areas and neuronal circuitries. Based on these findings, behaviorally derived theories suggest a failure in self-initiated control of activating task-specific brain regions [6]. This is in accordance with various findings that changed processing strategies in well-performing older adults may lead to normalized activation patterns.

On the other hand cognitive aging is also paralleled by overactivation of certain brain regions which is particularly the case for executive functions, motor control, and episodic, autobiographical and working memory [6]. It has been suggested that increased activity in PFC, as shown for a variety of tasks like face matching, lexical decision, word-pair encoding and retrieval, temporal-order memory, and verbal working memory, compensates for processing deficits in the sensory domain. The cost of such compensatory overactivation might be a reduction of cognitive resources available for task performance as formulated by the *resource competition hypothesis* or CRUNCH (*compensation-related utilization of neural circuits hypothesis*, [6]).

More task-specific age-effects include a decreased ►lateralization of the PFC. Whereas in young adults the left PFC is activated primarily in working memory tasks and the right PFC in visual attention tasks, in older subjects increased activity in the contralateral homologues regions of the PFC can be found. This *hemispheric asymmetry reduction in older adults* ("HAROLD", [5]) might be the consequence of compensation processes to enable normal cognitive functioning by recruiting contralateral resources. This view is supported by findings that asymmetry reduction mostly occurs in high-performing versus low-performing older adults or in successful versus unsuccessful trials.

On the other hand, decreased lateralization can be conceived as decreased specialization of brain processes reflecting difficulties in recruiting specialized neuronal processes (*De-differentiation hypothesis*, [7]). Thus overactivation might mirror decreased inhibition and inefficient processing. Supporting evidence comes from human imaging studies which show increased activations in perceptual areas and the anterior cingulate in tasks with conflicting conditions and from animal experiments revealing reduced tuning strength of neurons in the ►visual cortex and ►somatosensory cortex.

Morphological Changes of the Brain

During aging the average brain volume decreases from 1,300 grams at the age of 20 to 1,150 grams at the age of 80. This finding suggested that the number of cortical neurons declines with age and that this process is related to cognitive impairment. However, recent studies revealed that during normal aging there is – if at all – only a modest reduction in cell number of about 10% and it is now common sense that this decline is not significant for functional loss. This is in contrast to patients suffering from AD which in fact show cell loss rates between 30% and 50%. Even though white matter volume is reduced with age, possibly resulting in slowing of neuronal processing and deficits in its integrity, there is also no general reduction of axonal extent and dendritic branching as well as synaptic density. Thus, not the total number of neurons and their connections but the specificity of neurons and connections affected seem to be crucial for cognitive functioning.

PFC and MTL structures, for example, show more decline in brain volume and white matter integrity than other regions like sensory or ►motor cortices [4] and these changes are well correlated to deficits in executive control and memory processes. Animal studies reveal decreased dendritic branching of ►pyramidal neurons in the PFC and anterior cingulate but not the ►hippocampus ([8]). Specific effects also include the frontostriatal system resulting in decreased levels of neurotransmitters ►dopamine, norepinephrine and ►serotonin which in turn negatively influence the functional integrity of the PFC as supposed by the *dopamine theory of aging* (see [3]).

Other age-related changes of the brain include alterations in the brain hemodynamics and microvasculature. With aging, there can be found a general reduction of both the general cerebral blood flow (CBF) and the increase of local CBF accompanying neural activity. The resulting reduced hemodynamic response strength may be one cause for the cortical underactivation as measured with functional brain imaging. Interestingly, morphological changes do not inevitably correlate with alterations in neuronal activity. As outlined above, there is if at all only a modest decline in grey and white matter in the occipital cortex which, however, is characterized by decreased activation areas and response strength during visual processing tasks.

Neuronal Mechanisms of Cognitive Impairment

Aging rats are a well established model to study in vivo and in vitro cognitive processes at the neuronal level. Particularly, ►long-term potentiation (LTP) within the hippocampus plays a key role in spatial cognition and memory formation. LTP induction and maintenance is impaired in the hippocampus of aged rats. Possible explanations include reduced gene expression and protein synthesis, known to be crucial for LTP maintenance as well as changes in the Ca^{2+}-regulation, directly influencing ►NMDA-dependent plastic processes (for review, see [8]). Since the ►postsynaptic Ca^{2+}-concentration crucially affects the probability of the induction of either LTP or ►LTD (long-term depression), deficits in Calcium homeostasis may be the reason for an observed increased susceptibility of aged rats to LTD.

Also reduced ►neurogenesis in the hippocampus is associated with deficits in ►spatial cognition and memory formation. Interestingly, facilitation of neurogenesis in the hippocampus by, e.g., housing in enriched environments or regular physical activity (running in a treadmill) correlates with improved cognitive performance. Furthermore, spatial memory seems to be particularly sensitive to a loss of ►axodendritic synapses in the ►dentate gyrus. As a consequence of this decline in synapse number, field ►excitatory postsynaptic potentials are reduced in aged rats, thus increasing the threshold for induction of LTP [8].

Studies on the neuronal level outside the hippocampus are rare. Dinse and colleagues in detail investigated the functional properties of neurons and neuronal population in the somatosensory cortex of aged rats. Comparing young and old animals as well as different functional areas within aged individuals they were able to separate general age-dependent processes from those related to changed behavior during aging, the latter being reversible or at least subject to deceleration by normalization of behavior [9]. General age-dependent changes were reduced response strengths and prolonged latencies.

Resulting in impaired perception according to the hypothesis of cross domain resource competition these changes might lead also to cognitive impairment. On the other hand, decline of neuronal selectivity and topographic order, as well as reduced size of cortical activation areas correlated with changed behavior or disuse of body parts, resulting in reduced sensory experience with these body parts [9]. Taken together these studies reveal that not all changes in the brain during aging are due to general degenerative mechanisms but may be influenced by behavior.

The Role of Lifestyle for Preservation of Cognitive Performance During Aging

The high inter- and intraindividual variability of cognitive impairment during aging indicates that besides genetic predisposition individual lifestyle is a crucial factor. Cognitive training programs and active social involvement may stimulate functional plasticity and therefore compensation for cortical atrophy, white matter damage, and neurotransmitter dysfunction [6]. Even caloric restriction and cardiovascular fitness training have positive effects on cognitive functioning. Using functional MRI, Colcombe et al. could show that older subjects after a six months cardiovascular fitness program (walking) performed better in both simple and complex cognitive tasks with particular improvement in executive functioning. These behavioral effects were paralleled by significantly increased activity in PFC and parietal cortex and reduced activity in the anterior cingulate cortex which indicates a more efficient inhibition of task-irrelevant information [10]. Mechanisms of the relationship between cardiovascular fitness and cognitive functioning are not yet fully understood and still under discussion for different micro- and macroscopic levels of the brain. Besides neuronal survival and increased neurogenesis, possible mechanisms as revealed by animal experiments are increased angiogenesis in the capillary systems and thus improved blood supply, increased synthesis of synapses and neurotransmitters, and facilitation of gene expression and thus production of growth factors like ►BDNF and ►IGF-1. Not at last, physical fitness might prevent diseases like heart disease, hypertension, or diabetes which also have been related to cognitive decline. Taken together all these different processes further the brain metabolism and therefore improve cognitive performance.

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Cognitive Map

Definition

A mental map of space represented in an allocentric framework. The hippocampus is one brain region which has been defined as integral to spatial memory and a cognitive map theory in animals. Human cognitive mapping defined from cognitive psychology and geography involves extracting information from largescale environments to store in a mental representation of space.

►Spatial Cognition
►Spatial Memory

Cognitive Map Theory

Definition

The concept of a cognitive map derives from Kant's epistemology. Kant believed that humans and animals have innate perceptual schemes for processing sensory

information and that a geometrical-spatial framework is one of them. Tolman, an early twentieth century psychologist, pursued this notion and proposed that rats and other animals had cognitive maps that permitted flexible and efficient navigation. O'Keefe and Nadel, in the landmark book The Hippocampus as a Cognitive Map (1978), proposed the hippocampus as the neural substrate for the mapping system. Although hotly debated, the relationship of the hippocampus to the cognitive map remains a focus of current research.

►Spatial Learning/Memory

Cognitive Science

Definition

Scientific discipline, which developed in the second half of the twentieth century and integrates insights from psychology, linguistics, artificial intelligence, neuroscience, philosophy, and other disciplines to understand human cognition.

►Emergence
►Reductionism (Anti-Reductionism, Reductive Explanation)

Coherence

Definition

A function that shows the normalized relationship between two signals in the frequency domain.This function is similar to the cross-spectrum after normalization.

►Cross-spectrum
►Signals and Systems

Coherence Function

Definition

Coherence function refers to a normalized version of the cross-spectrum defining the linear relationship between two signals in the frequency domain.

Cold Pressor Test

Definition

The cold pressor test is a psychophysical protocol used to measure pain tolerance. The subject places a distal extremity in a circulating water bath maintained near 0° C. The duration of time that the person can keep his extremity in the water bath is the measure of pain tolerance.

►Pain Psychophysics

Collagens

Definition

Collagens are a family of glycoproteins that are the main proteins of connective tissue (cartilage, ligaments, tendons, bone and teeth) in animals and the most abundant proteins in mammals, making up about 25% of the total protein content.. Known for their tensile strength, collagens are made of three polypeptide chains, known as α-chains, which wind together forming a triple helix.

The different types of collagen arise from the fact that the α-chains differ in amino acid sequence and length (over 40 types of α-chains), allowing collagen molecules to be either homotrimeric or heterotrimeric.

►Articular Cartilage

Color Agnosia

Definition

Color agnosia is a difficulty in associating colors and shapes, e.g. to assign the color red to a black-and-white drawing of a strawberry. In order to associate a color with an object, these patients have to take deviant routes through other memorized associations.

Color Blindness

Definition

Group of inherited or acquired defects in ►color vision. Congenital defects include: anomalous protanomaly

with abnormal red-►cone pigment; anomalous deuteranomaly with abnormal green-cone pigment; anomalous tritanomaly with abnormal blue-cone pigment; dichromatopsia (with only two cones present) includes protanopia with missing red-cone, deuteranopia with missing green-cone, tritanopia with missing blue-cone; monochromatopsia (achromatic) in a typical form (all cones missing) and an atypical form (two cones missing). Acquired defects include tritanopia (►retinal outer-layer disease), protan-deuteran defects (retinal inner-layer disease), and normal with all three cones present.

Color Processing

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Synonyms

Color vision; Chromatic vision; Chromatic processing

Definition

Color is a sensation caused by the activation of *cone photoreceptors* (►Photoreceptors) in the ►retina and the subsequent processing of this activation pattern in the ►cerebral cortex. The physical property most closely related to color is the reflectance spectrum of a surface. Color as an estimate of the reflectance spectrum is an invariant object property and more than an aesthetic component of visual experience: Color facilitates object recognition (►Visual object representation) and plays an important role in scene segmentation and ►visual memory.

Characteristics

Color is a sensation, not a property of the physical world. It is often stated that color is closely related to the wavelength of light, but it has to be kept in mind that most illuminants and surfaces have broad spectra that contain many wavelengths. Furthermore, the perception of color (►color perception) depends to a large degree on other colors in the whole scene. By taking all colors into account, the visual system can discount changes in illumination (see below and ►Color constancy) and compute the object color that is closely related to the reflectance spectrum of a surface. Various stages of visual processing interact to extract a robust estimate of the reflectance spectrum that gives rise to the sensation of color.

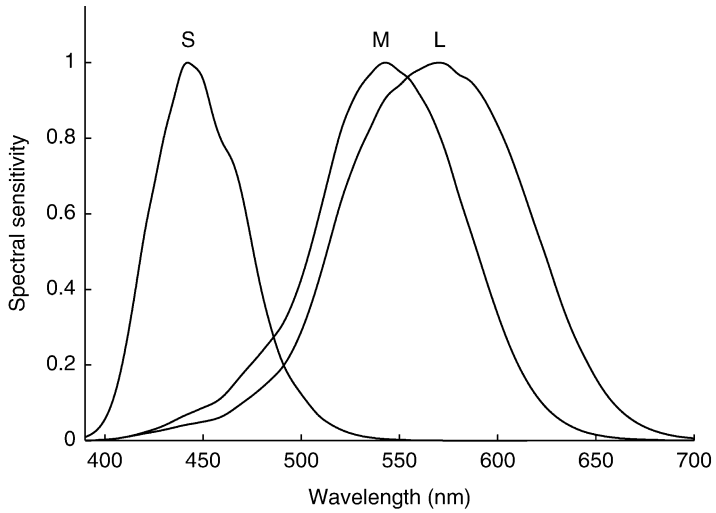
At the first stage in the retina, light is measured by three types of cone photoreceptors having different peak wavelength sensitivities. The cone responses are processed and recombined in the retina to form three channels, one purely achromatic channel and two chromatic channels. The visual input from the retina is transmitted in these three channels via the ►lateral geniculate nucleus (►LGN) to the cortex. In the retina and the LGN, neurons have a broad, linear wavelength tuning with peak sensitivities that cluster around two chromatic axes, L−M and S−(L+M), which are called "cardinal directions." Neurons with linear broad tuning curves are found at all stages, but the proportion of nonlinear neurons, narrowly tuned for color, increases along the visual pathway. Also, the peak sensitivities of cortical neurons no longer cluster. Instead, neurons sensitive to different chromatic directions exist, giving rise to multiple chromatic mechanisms. The multiple mechanisms are grouped at a higher stage, maybe in the ►inferior temporal cortex (IT), to form color categories. A specialized ►cerebro-cortical area devoted only to the processing of chromatic information has not been identified conclusively. Instead, color is processed at many stages and in many areas, involving – at different degrees – all visual cerebro-cortical areas.

Retinal Processing and Lateral Geniculate Nucleus

The retina is the first and best understood stage in color processing. Important constraints and transformations are of retinal nature [1].

At the first stage of color processing, electromagnetic radiation between 400 and 700 nm is absorbed by three different types of cone photoreceptors in the retina, with peak sensitivities at short (S, 430 nm), medium (M, 530 nm) and long (L, 560 nm) wavelengths [2]. The absorption spectra of the three types of cones are shown in Figure 1. The fact that humans have three types of cone photoreceptors is called ►trichromacy. Trichromacy is the reason why colors in any color space can be described by no more than three numbers.

The cones have overlapping sensitivity curves. The S cone photoreceptor absorbs light from 400 to 600 nm. The L and M cones have very similar absorption spectra that are broad and cover almost the entire visible spectrum. Already in the retina, the three classes of cones are recombined in three anatomically and physiologically distinct paths. One path pools activity from L and M (and maybe also S) cones and signals achromatic luminance. The two other paths are cone-opponent and form the basis of color vision. The two cone-opponent paths are sometimes referred to as L−M and S−(L+M) and define together with the luminance pathway the cardinal directions of the DKL color space [3]. The cone-opponent channels are sometimes referred to as "red-green" and "blue-yellow." These labels are misnomers for two



Color Processing. Figure 1 Cone absorption spectra.

reasons: First, neurons in the L−M path respond both to color and luminance [4]. For example, a L−M single opponent cell responds best to a white spot on a black background and to a uniform red region. Second, the unique hues (red, green, yellow and blue) do not emerge in the retina: Colors along the L−M channel vary between a pinkish-red and a bluish-green, and colors along the S− (L + M) channel vary between a yellowish green and purple.

The cardinal directions correspond to anatomically and physiologically distinct pathways. The L + M or ►magnocellular (visual) pathway carries only achromatic information, is fast and transient (M-cells, Y cells in the cat). The L−M ►parvocellular (visual) pathway (P-cells, X cells in the cat) transmits L and M cone-opponent signals. Due to the ►antagonistic center-surround arrangement of the ►receptive fields (►Visual cortical and subcortical receptive fields), neurons in the parvocellular pathway transmit both chromatic and achromatic signals. Chromatic signals are transmitted with a low-pass characteristic and achromatic luminance signals with a band-pass characteristic. Input from the S cones is processed by bistratified ganglion cells and feeds the ►koniocellular (visual) pathway (►Retinal ganglion cells; ►Geniculo-striate pathway).

Cortical Processing and Higher-Order Mechanisms

The properties of the neurons in the retina and the LGN have been studied in great detail and are well understood. The properties of cortical neurons at subsequent "higher-order" stages of cortical processing are less clear and a subject of intense research [5].

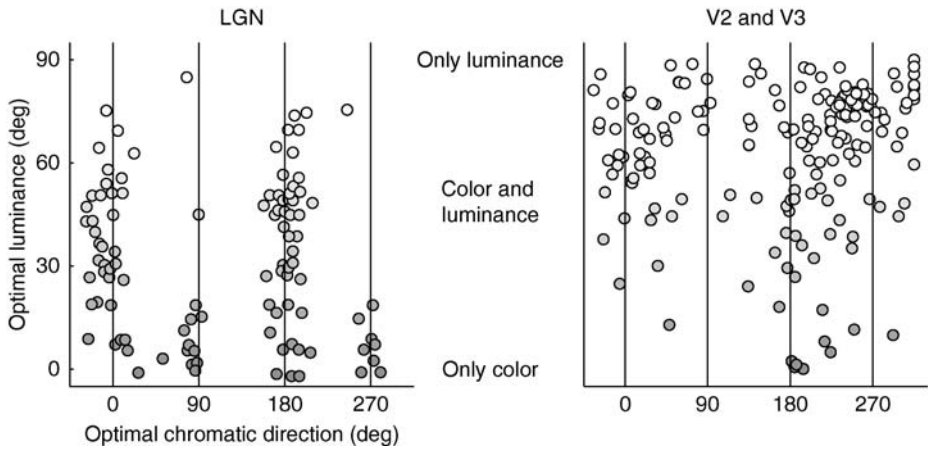
Chromatic mechanisms are typically characterized by their number, tuning peak direction, and tuning width. Subcortical neurons in the retina and the LGN have peak sensitivities that cluster along the cardinal directions (Fig. 2, left). Tuning curves of neurons in the retina and the LGN are broad, consistent with a linear transformation of cone inputs.

How do these properties of neurons change during further processing? First, peak sensitivities of cortical neurons do not cluster, but have a continuous distribution (Fig. 2, right). Second, neurons with narrow tuning curves are found. Broad tuning curves still occur at all levels of processing, but the proportion of neurons with a narrow tuning width increases as the processing proceeds along the hierarchy of visual areas. Narrow tuning widths indicate a nonlinear transformation of cone inputs. Third, ►double-opponent cells are found. A double-opponent cell can signal the color contrast independent of the illumination and presumably plays an important role in color constancy.

Segregation and Integration

One of the most fundamental questions of cortical processing is whether visual attributes such as form, color and luminance are processed in segregated visual processing streams or together (►Visual processing streams in primates; ►Extrastriate visual cortex). At the level of the retina and the LGN, chromatic and luminance signals are processed together by cells of the parvocellular pathway. A P-cell responds both to an achromatic luminance contrast (band-pass) and to a homogeneous color (low-pass).

Early hypotheses about the further cortical processing have often favored the wrong idea of a neatly segregated processing of color and luminance. For example, the coloring book theory assumes that first a sketch of achromatic edges of the scene is extracted, that is subsequently colored by chromatic surface information.



Color Processing. Figure 2 Color and luminance preferences of neurons in the LGN and in the cortex (►areas V2 and V3). The *x*-axis denotes the optimal chromatic direction as azimuth in the isoluminant plane of the DKL color space, the *y*-axis denotes the preferred luminance as elevation above the isoluminant plane. Neurons in the LGN cluster around the cardinal directions, neurons in the cortex do not. Most neurons in the LGN and the cortex respond to both luminance and color.

Recent physiological findings have consistently drawn a different picture. Most neurons in ►area V1 (primary visual cortex, striate cortex, Brodmann´s area 17) are color-luminance cells that respond best to an oriented contrast (►Visual cortical and subcortical receptive fields; ►Geniculo-striate pathway), defined by a combination of color and luminance.

Likewise, the idea that color-preferring cells are localized preferentially in the ►blobs has not been confirmed by recent findings. The wrongly presumed separation in area V1 has been hypothesized to occur also in ►area V2. However, a meta-analysis of six studies investigating color and orientation preference in different compartments of macaque monkey area V2 reveals a combined processing of color and orientation. Further it has been shown that the vast majority of color-selective neurons in areas V1 and V2 are also selective for orientation. Recent physiological findings consistently show that at the early cortical stages color, luminance and orientation are processed together by the same neurons [5].

Color Appearance

The appearance of a color can be described along three perceptual dimensions, namely hue, saturation, and brightness. Hue is the dimension commonly referred to as color, changing along a color circle from, e.g. red through orange, yellow, green, blue, purple back to red. Saturation is the perceptual difference from an achromatic color (black, gray, white). Brightness is the perceived achromatic intensity.

There are 7–11 basic color terms, which agree remarkably across many cultures. The English names for these basic color terms are black, white, red, yellow, green, blue, brown and orange, pink, purple and gray. Some languages deviate from this scheme, such as Russian having not a single name for blue but two for light and dark blue, while other languages merge blue and green into a single "grue" category.

Color appearance and processing is influenced by higher-level factors such as ►memory and language. The color appearance of a familiar object with a distinct object color is biased towards the object color. For example, fruit images appear neutral gray only when tinted with the color that is opponent to the object color [6]. The involvement of language in color processing results in faster discrimination across color categories [7]. Modulating feedback-connections could provide the neural substrate of these higher-level influences on color processing.

Color Constancy

Color constancy is the ability to assign a constant color to objects independent of changes in illumination. If we look at a blue object under daylight, the object reflects mainly short wavelengths. The same object when illuminated by a light bulb reflects more light of longer wavelengths. Despite such gross reflection changes the object consistently appears blue. The remarkable feat of the visual system is to somehow "discount the illuminant" and to estimate the surface reflectance as an invariant object property. How can this ability of the visual system be achieved? The light reflected from an object depends both on the spectral reflectance properties of the surface and on the spectral distribution of the illumination. To disentangle the effects of illumination and surface reflectance the visual system needs more

than one source of information. Many potential cues can be used such as local edge contrast between different surfaces, global average of a scene, knowledge about the three-dimensional arrangement of a scene, or knowledge about the typical color of an object [8].

One possible neural substrate in the cortex involved in color constancy are double-opponent cells. Unlike single-opponent cells in the LGN, double-opponent cells signal the color contrast of the center relative to the surround. Double -opponent cells have been found in area V1 [9]. Another cortical area presumably involved in color constancy is ►area V4. Neurons in area V4 shift their color-tuning profile with a change in background illumination, as required for color constancy [10].

►Retinal Color Vision in Primates

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Color Vision

►Color Processing
►Retinal Color Vision in Primates

Colubridae

Definition

A family of snakes; beside many harmless snakes, as grass snake, Aesculapian snake, it comprises, according to some taxonomy, cobras and coral snakes as well.

►Evolution of the Brain: At the Reptile-Bird Transition

Columella

Definition

Single middle ear ossicle of sauropsids, homologue of the mammalian stapes (stirrup).

►Evolution of the Auditory System in Mammals

Columnar Structures

Definition

Hypothetical structures that are parpendicular to the cortical surface and are assumed to be a functional unit of the neocortex.

►Somatosensory Cortex I

Coma

Definition

Coma denotes a patient's state, from which he/she cannot be aroused even by strong stimuli and makes no attempt at avoiding them. It may be caused by destruction of certain areas in ►brainstem and ►cerebral cortex (anatomical coma) or by disturbances of metabolic processes (metabolic coma). The latter may come about by ischemia, hypoxia or hypoglycemia, or by drug/alcohol intoxication, toxic endogenous metabolites (associated with hyponatremia, hyperosmolarity, hypercapnia; metabolic encephalopathies of hepatic and renal failure, hypercalcemia, hypothyroidism, vitamin B12 deficiency, hypothermia), or ►epilepsy.

Combinatorial Coding

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Synonyms

Spatial coding; Binding; Sparse coding

Definition

One of the fundamental concerns of neuroscience is the data structure or the code by which the brain represents information about the outside world. Evidence has accumulated that such information is encoded in the pattern of neuron electrical activity. A number of coding schemes have been proposed to explain how neurons represent, store, recall and manipulate "information" about outside world, and most of them share a common principle: they correlate various temporal and spatial aspects of the neuronal representation with the features of the stimuli.

The basic tenet of perception is that the different aspects of "natural objects" (color, shape, odor, etc.) are processed separately in specialized sets of neurons and then combined to form a unified perceptual experience. The question is then how the nervous system can cope efficiently with the complexity of the combinatorial environment: complex objects and situations are constructed by combining simpler elements, the diversity of such combining being virtually unlimited [1]. Understanding how neuronal networks perform such a task remains a challenge, but many agree that combinatorial codes that use the "power of combinatorial arrangement" to counterbalance the combinatorial complexity of the environment is, among others, a strategy that could be used by the brain. Consider that a given "feature" of an object is coded by units that are, for the sake of simplicity, either "active" or "passive"; combining N such units leads to $c = 2^N$ possible combinations ($c = 1024$ if $n = 10$). This number grows exponentially with increasing N ($c > 1^{301}$ for $n = 1000$). A combinatorial coding is then based on the activation of specific combinations of identified units. Depending on the stimulus, the number of active units could vary from 1 to N. This is different from local coding where only one unit is activated and sparse coding where the amount of active units is small compared to their total number [2].

Characteristics

Description of the Process: The Olfactory System Case

Humans can distinguish a huge number of volatile chemicals, typically small organic molecules that vary in a number of parameters (size, shape, charge) and chemical structure (alcohols, aldehydes, esters, aromatics, alicyclics, etc.). Odors are detected initially at the level of odorant receptors located on the cilia of olfactory sensory neurons in the olfactory epithelium of the nasal cavity. In mammals, the total number of genes coding for odorant receptors varies across species, with, for example, around 1,000 functional genes identified in mice, whereas around 400 have been identified in humans. The question then is – how can many thousands of volatile chemicals be perceived and discriminated with so few odorant receptors?

It has been proposed that the sense of smell in mammals is based on combinatorial coding. That is, instead of dedicating an individual OR to a specific odor, the olfactory system uses combinations of receptor types to greatly reduce the number of receptors required to convey a broad range of odors. That is:

1. A single receptor can recognize multiple odorants, indicating that the system is not based on a strict specificity "one odorant = one receptor."
2. A single odorant is typically recognized by multiple receptors.
3. In contrast to the genetic code where several "words" have the same meaning (different codons can specify the same amino acid), coding of odorants does not seem to be degenerated, that is different odorants are recognized by unique combinations of activated receptors.

These results illustrate how the specific detection of an odorant can be achieved using a device of low specificity (a single odorant receptor recognizes multiple odorants). The functional overlap among receptors and their low specificity is exploited to expand the coding capacity of the system by allowing for combinatorial coding. Specificity is achieved through the combination of responses of several receptors.

In mammals, information carried by odorant receptors are summarized within a spatial organization and specific ►oscillations. Axon terminals from olfactory sensory neurons that express the same olfactory receptor converge in the olfactory bulb on spherical structures known as glomeruli. The olfactory sensory neurons synapse with the dendrite of mitral cells, which in turn output to the olfactory cortex. Then mitral cells in a given glomerulus form their responses to a given odor from very large numbers of converging sensory inputs, ensuring the reliability of the transmission of the information [3,4]. Signals from different types of olfactory sensory neurons are sorted into different glomeruli and a given odorant object is coded by a specific combination of activated glomeruli. In such a way, combinatorial activation of glomeruli defines a two-dimensional map in the olfactory bulb which "shows" which of the olfactory receptors have been activated within the sensory epithelium. Discrimination

of odor then results from the spatial coordinates of the activated glomeruli.

The combinatorial problem is not only due to the large number of chemical components, but also to the huge number of possible mixtures of these components. To cope with the problem of mixtures, any combinatorial system needs mechanisms that allow the neural instantiations of the different elements to be related temporarily in such a way that the relations between the constituents are preserved.

Intensity and Mixture Recognition With Combinatorial Coding

Information about odor composition or intensity is of great significance for behavior. For example, the ability to discriminate intensity is essential for successful navigation toward odor source or for detection of a predator's odor from the ambient one. In terms of perception, combinations of many individual compounds can be perceived either as new odorants or as a sum of odorants. Furthermore, the same odorant can be perceived similarly or differently depending on its intensity: thiols, for instance, have a strong, repulsive smell that is obnoxious at high concentrations, but is perceived as a sweet citrus aroma when diluted. However, most odors maintain the same quality over orders of magnitude of concentration. If the quality of an odor is reflected in the combination of responses of several receptors, then this raises the problem of superposition. Distributed representation of information by coactive neurons leads to the classical "superposition catastrophe". Consider an assembly of coactive neurons activated by stimulus X and another one by stimulus Y. If both stimuli come together, it would be impossible to distinguish the two assemblies, as information on their membership in the original sets is lost [1]. To avoid such problems, the co-activation induced by compound elements should be different from the sum activation induced by individual elements. In such a way, downstream circuits can benefit by interpreting patterns of activation as distinct coding symbols, that is, each combination can be handled as a unit having an explicit structure allowing comparison, classification, and decomposition.

Experimentally, it has been found that the number of glomeruli that are activated by a single odorant depends on its concentration, suggesting that this number would allow a precise assessment of an odorant's concentration. At a relatively high concentration, simple chemical compounds activate specific but large subsets of receptor types [5]. A simple additive reasoning would suggest that natural odorants, which are each composed of hundreds of simple chemicals, would therefore lead to the recruitment of large and overlapping fractions of glomeruli, a condition that would entail a combinatorial code to avoid "superposition catastrophe". However, a recent experiment with complex odorants at their natural concentrations shows that only a small fraction of the glomeruli are activated, suggesting a "sparse coding" in natural conditions [6]. This is possible because a mixture seems to be identified by specific and strong responses to only a small number of its constituent chemicals. The response induced by a mixture is then the sum of the responses to specific individual constituents. Sparse coding prevents overlapping and reduces the risk of superposition catastrophe, however it also reduces the coding capacity of the system, raising the question of the capacity of the system to code for the large number of volatile odorants. Furthermore, sparse coding is linear while combinatorial is not, and as indicated above, the perception of complex odorants can be different from the simple superposition of components. It could be the consequence of processing that occurs in a higher brain area, but other mechanisms that take place at the level of the olfactory bulb can also be invoked.

Combinatorial Coding and Dynamics

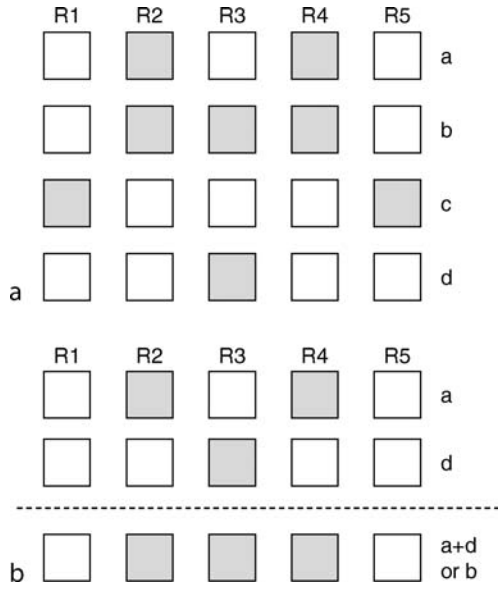
Depending on its composition, a given odor will activate a specific combination of glomeruli. A reasonable question would then be whether a code based on an "all or none" activation of combinations of glomeruli is sufficient to represent all the olfactory information that an animal processes in its lifetime. Furthermore, the assumption that specific combinations are available when and where required could be problematic. Finally, the "spatial" view of the coding is rather static and all notion of learning, for example, is removed. Recent studies indicate that the spatial pattern of bulbar activity is not only distributed, but also extremely dynamic. Dynamics provide a set of mechanisms by which the glomeruli repertoire of activation can extend the "coding capacity" of the olfactory system. Such coding encompasses various aspects that are all related to combinatorial coding.

First, it should be noted that the sampling of the "olfactory world" is not a continuous process. In mammals, the sense of smell relies on sniffing, and as a consequence, the world of odors is conveyed in discrete samples, i.e. olfactory "snapshots" [7]. This active sampling of the environment also exists in fishes, crustaceans and insects. In rats, experimental evidence has shown that a correct discrimination of two subtly different odors activating largely overlapping glomerular representations can be achieved within one sniff that is in less than 200 ms. These place a necessary temporal constraint on the overall processing time that is available to interpret the spatial code of activity. Even if it is clear that discrimination might benefit from larger integration times, a trade-off between accuracy and detection of a new odorant or gradient of odorant has

to be found. Overall, it appears that olfactory discrimination is fast and probably occurs within a sniff (Fig. 1).

Combinatorial coding is based on a differential activation of glomeruli (or of receptors) and a simple scheme would be that mitral cells or their equivalent in non-mammal systems respond to an odorant either by no change in activity or by an increased firing rate. A number of laboratories have recorded the electrophysiological activity of such cells and a simple rate coding (increase or decrease of number of action potential per window of time) does not seem to be the rule. In addition to the spatial aspect of odor representation, it has been suggested that glomerular activation maps also contain reliable stimulus-specific sequences of action potential patterns [8] or sequences of onset times [9]. In the drosophila antenna, it has been suggested that receptors confer not only the odor but also the response mode and the response dynamics upon the olfactory sensory neurons that express them, as well as the level of spontaneous activity. Coding is then expanded by the multiplication of response characteristics exhibited by each receptor.

Finally, it has been proposed that the nervous system uses spatiotemporal patterns of neuronal activation to create a large coding space. In such a view, the odor is encoded not in the topography, but in the temporal dynamics of the action potentials elicited by different odors [10].



Combinatorial Coding. Figure 1 (a) Pattern of activation of receptors or glomeruli (represented by a square): A particular odor compound (labeled a, b, c or d) is coded according to which receptors are activated, as indicated by color (white represents no activation). Four odor compounds are depicted with the specific array of receptors each would activate. (b) If two sets of active neurons (a and d) are simultaneously activated (panel above dashed line), information on their membership in the original sets is automatically lost.

Conclusions

At first sight, the olfactory system uses a relatively straightforward strategy based on combinatorial coding for perceiving and discriminating odorant molecules. Combinatorial coding seems appropriate when the purpose of the system to be modeled is feature detection, but seems more problematic when it is a general purpose device. Indeed, to be exploited in other contexts, any experience gained in a particular circumstance should be affixed to the most general description of the situation [1]. Most of the neurophysiological evidence deals with sensory detection of odors that is the association of a given odorant with a sole pattern of activity in the olfactory system ending into the orbitofrontal cortex (►cortex orbitofrontal), leaving aside the interpretation of odors and how this directs behaviors. Such a role is supposed to be attributed to the brain cortex, but opinions differ on the extent to which it could begin in the olfactory bulbs themselves.

Finally, it should be stressed that all odors in our environment are certainly not processed using the same coding strategy. During an animal's life some odors have to be learned, others not. Combinatorial codes can be envisioned for odors that are characteristic of a given species. Indeed, most animals have innate behaviors that are associated with given odors and it has been demonstrated that a single type, but also a few types, of receptor acting combinatorially mediate robust behaviors in drosophila. Overall, much remains to be understood about the detailed mechanisms of odor perception, but these mechanisms are certainly shaped by the specificity of olfaction. If light or sounds are constant physical stimuli, the world of smell varies with evolutionary time [3].

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Combinatorial Transcription Factor Codes and Neuron Specification

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Synonyms

Transcription factor codes; Combinatorial action of transcription factors; Neuronal determination; Neuronal differentiation

Definition

A "combinatorial code" of ▶transcription factors is commonly used to refer to two related phenomena in the specification of neurons:

1. Cellular definition. i) A combination of transcription factors that is required together to activate or repress a certain gene in a certain cell. ii) A combination of transcription factors that is required together to execute a neuron's distinct differentiation program.
2. Developmental definition. i) The difference in the combination of transcription factors, between neurons, that accounts for their distinct gene expression profiles. ii) A spatial or temporal transition in transcription factor expression that confers a distinct program of neuronal differentiation or gene expression.

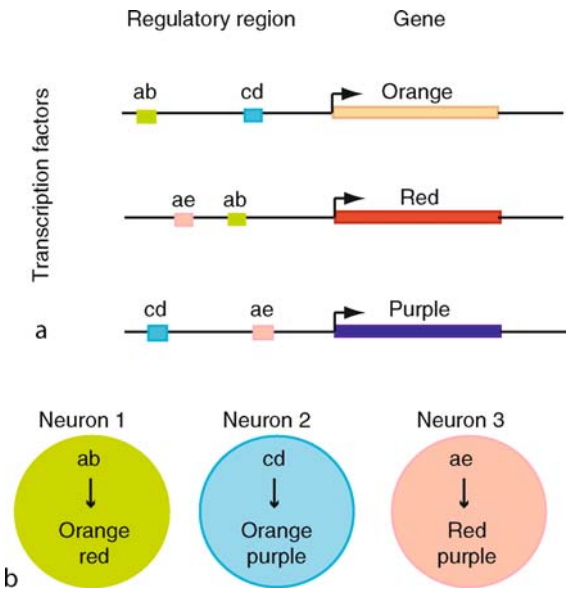
Characteristics

The nervous system contains many different types of neurons, whose differences ultimately reside in their distinct gene expression profiles. This essay outlines how the deployment of specific combinations of transcription factors in neuronal progenitors and ▶post-mitotic neurons direct the execution of distinct programs of neuronal differentiation. Discussed here are the functions of these transcription factors from the perspective of their acting in "combinatorial codes" that diversify neuronal gene expression profiles.

Combinatorial Codes and *cis*-Regulatory Modules

Transcription factors are proteins that bind DNA at specific sequences (termed transcription factor binding sites - TFBS) in a gene's ▶regulatory region, from where they modulate (activate or repress) activity of the gene's ▶promoter. TFBS are clustered into *cis*-regulatory modules that bind specific combinations of 2–10 transcription factors. By clustering TFBS for different transcription factors, *cis*-regulatory modules are a critical platform for decoding cell-specific combinations of transcription factors into cell-specific patterns of gene expression [1].

Efforts to unravel the organization of *cis*-regulatory modules in *C.elegans* neurons have proven illuminating [2] (Fig. 1). Most of the genes expressed in AIY neurons (sensory processing neurons) are activated by the combinatorial action of the LIM-▶homeodomain transcription factor TTX-3 and the Paired-homeodomain transcription factor CEH-10. These factors bind cooperatively to a 16bp *cis*-regulatory module in the regulatory



Combinatorial Transcription Factor Codes and Neuron Specification. Figure 1 *Cis*-regulatory modules respond to different combinations of transcription factors to assign gene expression to specific neurons (a) Three genes – orange, red and purple – that have an array of *cis*-regulatory modules (coloured boxes) in their regulatory region. *cis*-regulatory modules bind to a certain combination of transcription factors (a + b, or c + d, or a + e). Arrow denotes the gene's promoter. (b) Neuron 1 expresses transcription factors a + b. This combination activates the orange and red genes because those genes contain a *cis*-regulatory module that binds the a + b combination of transcription factors (in a). A similar rationale controls gene activation in neurons 2 and 3.

region of most AIY-expressed genes, and that is necessary and sufficient for gene expression in AIY neurons. This work also found a simple mechanism for gene expression in different neurons. Each gene has an array of *cis*-regulatory modules. Each module assigns expression of the gene to a different neuron - by binding the combination of transcription factors in that neuron [2] (Fig. 1).

This elegant organization has been elaborated upon by evolution. First, *cis*-regulatory modules can be more complex. The expression of a single gene in a single cell can require the binding of eight or more transcription factors to TFBS, which are not all clustered into one module [1,3]. Second, the genes expressed in a single cell are often not all controlled by the same combination of transcription factors. For example, the two subunits of luteinizing hormone are controlled by different combinations of transcription factors in the same cells - pituitary gonadotrophs [3]. More examples are outlined below; "Transcriptional sub-programs in neurons."

In the era of genomic sequencing, researchers are taking advantage of TFBS clustering and the sequence-specificity of transcription factor binding to develop methods for identifying and studying gene regulatory elements of genes [4]. These efforts are providing a wealth of new data and highlight how little we currently understand.

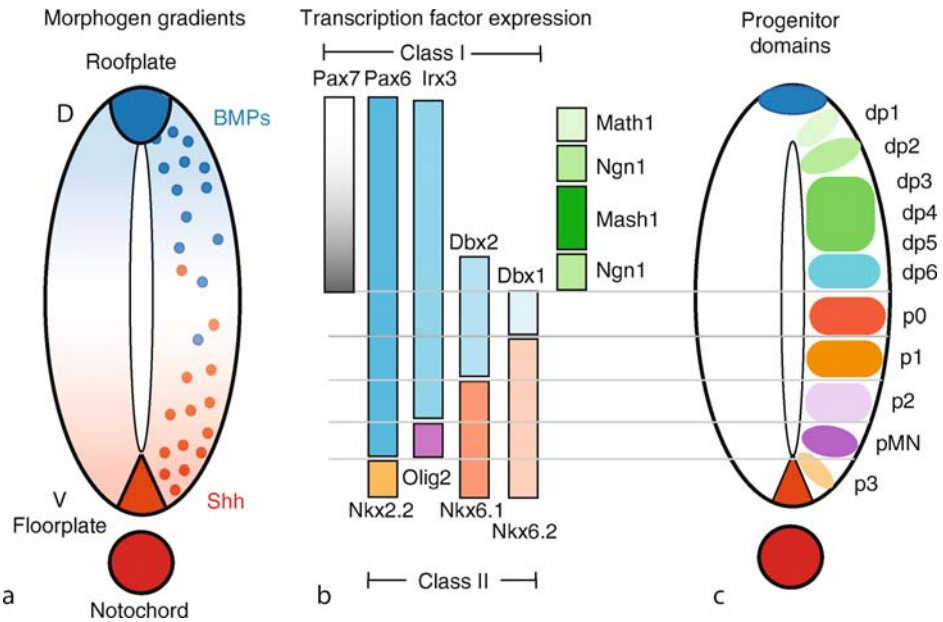
Combinatorial Codes in Neuronal Differentiation

Neuronal differentiation starts in ►progenitor cells that translate extrinsic "positional" cues, related to the body plan, into the regionalized expression of different combinations of transcription factors [5] (Fig. 2).

These factors initiate hierarchical transcriptional cascades that diversify those progenitor populations, culminating in the generation of post-mitotic neurons endowed with different combinations of transcription factors [5]. Each cell-specific combination of transcription factors then activates a ►cell-specific battery of terminal differentiation genes, which shapes the neuron's distinct form and function [1,2,5].

Spatial combinatorial codes translating axial cues into progenitor domains

The chick and mammal neural tube emerges as a field of ►multipotent neuroepithelial cells. In the early spinal cord, these cells are regionalized along the



Combinatorial Transcription Factor Codes and Neuron Specification. Figure 2 Generation of a spatial combinatorial code of transcription factors in the developing spinal cord from apposed gradients of two morphogens. Cartoons representing a transverse section through the developing spinal cord. (*D* dorsal; *V* ventral) and the expression domains of transcription factors in progenitor cells. (a) The developing spinal cord is patterned along the dorsoventral axis by apposed gradients of bone morphogenetic proteins (BMPs), secreted from the roof plate, and Sonic hedgehog, secreted from the notochord and floorplate. b) In response to the local level of Shh and BMPs, a set of homeodomain and bHLH transcription factors become expressed in specific domains. Transcription factors apposed vertically are mutually repressive. A set of BMP-activated bHLH transcription factors are shown in green boxes. (c) The combinatorial expression of these transcription factors define domains of progenitor cells (their names are on the right) that will give rise to distinct types of neurons. Additional transcription factors contribute to this spatial code, but are omitted here for clarity.

dorso-ventral (D-V) axis by apposed gradients of secreted Sonic hedgehog (Shh) and bone morphogenetic proteins (BMP). Progenitors transduce their position along this gradient into the expression of different homeodomain and basic helix-loop-helix factors [5] (Fig. 2). Coordinately, the antero-posterior (A-P) axis is set up by gradients of secreted retinoic acid, fibroblast growth factors and Wnts. Progenitors transduce their position along this axis into expression of different homeodomain Hox factors.

Patterning of the ventral-half spinal cord by Shh is well-studied [5]. Shh, secreted from the ►notochord and ►floorplate, establishes a D-V gradient that is translated into five expression domains of mainly homeodomain transcription factors by the following mechanisms: i) Shh represses Class I transcription factors (Pax6, Irx3, Dbx2, Dbx1 and Pax3/7), and activates Class II transcription factors (Nkx2.2, Olig2, Nkx6.1 and Nkx6.2). ii) Each of these factors responds at a different threshold (step) of the Shh gradient. At each step, a single Class I factor is repressed (limiting further ventral expansion), and a single Class II factor reaches its threshold for activation (limiting further dorsal expansion). iii) Class I and II factors, whose limits of expression coincide at a single step, mutually antagonize one another's expression. This sharply delineates the borders of each factor's expression domain. This spatial combinatorial code of transcription factors commits progenitor cells to distinct neuronal differentiation programs [5]. For example, loss of Nkx6.1 expression allows ventral expansion of its repressive partner, Dbx2. This re-specifies progenitor cells that normally express Nkx6.1 (that would differentiate into ►motoneurons or V2 interneurons) into progenitor cells that now express Dbx2 (and that now differentiate into V1 interneurons). These early transcriptional codes act via primarily repressive mechanisms, suggesting that neuronal fate assignment in progenitors is largely determined by the progressive restriction of alternate fates [5,6].

From invertebrates to vertebrates, equivalent mechanisms exist throughout the nervous system to regionalize the differentiation of specific types of neurons. Remarkably, the involvement of many of the secreted axial cues and transcription factors are conserved [6].

Combinatorial codes that diversify neuronal subtypes

The emergence of distinct neuronal subtypes from progenitor cells entails hierarchical, combinatorial cascades of transcription factors [5,6,7,8]. Vertebrate motoneuron differentiation from pMN progenitors in the spinal cord is well studied [5,6]. The Shh gradient establishes Pax6 and Nkx6.1 expression in pMN progenitors. These act combinatorialy to activate Olig2 expression only in pMN progenitors. The combined action of Olig2 and Nkx6.1 then promotes expression of the ►bHLH transcription factor, Ngn2. In the context of Ngn2 expression, Olig2 then promotes expression of the homeodomain factors Lhx3, Isl1 and HB9 (and MNR2 in chick) and the bHLH factor NeuroM, around the time of motoneuron birth. This combination of transcription factors is then critical for executing a motoneuron-specific program of differentiation. The combinatorial nature of Olig2 function is underscored by events that occur after motoneuron birth. Remaining pMN progenitors switch from Olig2/Ngn2 co-expression to Olig2/Nkx2.2 co-expression. This re-commits pMN progenitors from motoneuron differentiation to an oligodendrocyte differentiation program. This type of hierarchical transcription factor cascade is a common theme for neuronal differentiation from progenitor populations in the nervous system of all organisms [2,5,6].

Expression of HB9, Islet1 (Isl1), Lhx3 and NeuroM (and MNR2 in chick) around the time of cell-cycle exit is critical for motoneuron differentiation. Islet1, Lhx3 and NeuroM combinatorialy activate and ensure maintained expression of HB9. In turn, HB9 (and chick MNR2) promotes Isl1 and Lhx3 expression. This type of positive feedback mechanism that consolidates the robust expression of a cell-specific transcription factor code has been observed in neurons of all organisms [2,5,6].

After motoneuron birth, the LIM-homeodomain transcription factor family (Isl1/2, Lhx3/4, Lhx1) subsequently acts to diversify motoneurons into distinct subtypes with different axon pathfinding trajectories [4]. Vertebrate spinal motoneurons maintain HB9 and Isl1expression, however, the other LIM-homeodomain transcription factors (Islet2, Lhx1, Lhx3 and Lhx4) become differentially expressed in the different motoneuron subtypes. Experimental manipulation has demonstrated the functional relevance of this so-called LIM-code. For example, Isl1/Lhx3-expressing motoneurons pathfind within the dorsal ramus to axial muscles whereas Isl1-only motoneurons pathfind within the ventral ramus. Lhx3 overexpression forces Isl1-only motoneurons to pathfind into the dorsal ramus. Similarly, Lhx1 acts combinatorialy with Isl1 to control innervation of the dorsal vs. ventral half of the limb bud. The function of the HB9/LIM-homeodomain combinatorial code for motoneuron differentiation is remarkably well conserved from *Drosophila* to mammals [5,6]. However, in spite of some progress in defining the genes downstream of these combinatorial codes, this persists as an important challenge.

Some progress has been made in elucidating the biochemical nature of these combinatorial codes. The functional significance of the Isl1/Lhx3 code has been tested for V2 interneuron versus motoneuron differentiation [5]. V2 neurons arise from p2 progenitors, which reside in the domain adjacent to pMN progenitors

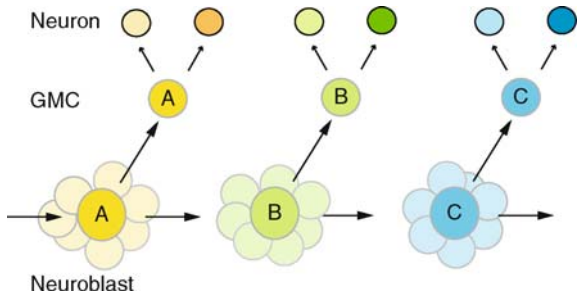
(those that generate motoneurons) (Fig. 2). Around the time that p2 and pMN progenitor cells undergo their final round of cell division, Lhx3 is expressed in p2 progenitors, whereas Isl1 and Lhx3 are co-expressed in pMN progenitors. In p2 cells, a complex comprising two Lhx3 proteins - bridged by the self-dimerizing NLI cofactor (Lhx3-NLI:NLI-Lhx3) – is formed. In pMN cells, a complex of Islet - bridged by the NLI dimer – is formed. Lhx3 then binds to the apposed Isl1 proteins to form a pMN-specific complex comprising Lhx3:Islet-NLI:NLI-Islet:Lhx3 [5]. Experimental manipulation of these complexes have proven their functional potency in promoting p2 to V2 differentiation versus pMN to motoneuron differentiation. The Pfaff Lab subsequently demonstrated that motoneuron-specific activation of HB9 depends upon the binding of the Lhx3:Islet-NLI:NLI-Islet:Lhx3 complex to a *cis*-regulatory module in the regulatory region of the HB9 gene. The activity of different transcription factor complexes at discriminatory *cis*-regulatory modules is proving to be a common mechanism for exerting unique transcriptional readouts from subtly different combinations of transcription factors.

In contrast to earlier-acting transcription factors that act largely as repressors, many factors acting in post-mitotic neurons are activators of gene expression [2,5,8]. Interestingly, when misexpressed, certain post-mitotic transcription factor codes can trespass upon earlier-acting codes to dominantly impose their own late program of terminal differentiation [8]. Does this indicate that early-acting codes merely act to establish late-acting codes, which then execute the program of terminal differentiation? It is unlikely this simple. Examples from all model organisms show that certain early-acting factors persist to play critical roles in later-acting combinatorial codes, a concept termed "combinatorial feedforward coding" [8]. Further research will likely illuminate the temporal function of individual factors acting within the transcriptional cascades that shape neuronal differentiation.

Temporal Combinatorial Codes that Transition Progenitors between Competence States

A common mechanism for generating neuronal diversity is to progressively alter the competence of progenitor pools, or neuroblasts, to produce different types of neurons at specific timepoints [9]. Within a single lineage, certain transcription factors become expressed at different steps of lineage progression, that alter the program of neuronal differentiation (Fig. 3).

Drosophila neuroblasts undergo an invariant series of cell divisions, each time generating a neuroblast and a ganglion mother cell (GMC). The GMC subsequently divides once to produce two post-mitotic cells. The first neuroblast expresses Hunchback. When this neuroblast divides, it produces a daughter GMC and a daughter



Combinatorial Transcription Factor Codes and Neuron Specification. Figure 3 A temporal code of transcription factors that generates distinct neurons from the same neuroblast or progenitor pool. Neuroblast A represents a neuroblast or progenitor pool (lighter cells) within a specific lineage that expresses the temporally-encoded transcription factor A. Upon a round of cell division, neuroblast A produces a daughter ganglion mother cell (GMC), with the same transcription factor A, and a daughter neuroblast, which expresses transcription factor B, instead of A. For progenitor pools, transitions in transcription factor expression can be regulated by feedback from the neurons produced at each timepoint. The result is a diverse set of neurons that were produced from the same lineage.

neuroblast. The GMC expresses Hunchback. However, the daughter neuroblast expresses Kruppel, rather than Hunchback. Upon division of this new neuroblast, the daughter GMC expresses Kruppel but the daughter neuroblast expresses Pdm. Subsequent division results in Pdm in the GMC and Castor expression in the daughter neuroblast. Studies on Hunchback and Kruppel have shown that these transcription factors function to change the program of differentiation of each GMC, resulting in the production of different neurons. Although there can be some variability between lineages, many different neuroblast lineages utilize this same code. Thus, the temporal code acts in the context of distinct lineage-restricted transcription factors to diversify the neurons produced by each lineage [9]. Similar events occur in the vertebrate retina where a common progenitor pool produces all neuronal types of the retina by undergoing temporally-encoded changes in transcription factor expression, each of which results in the generation of a particular type of neuron [9].

There is less information regarding how successive transitions in temporal cues are controlled. Work in the vertebrate retina has provided evidence for feedback from recently born cells that instruct progenitors to transition. Implicated signaling pathways include cytokines, BMP-type signals and Sonic hedgehog [9]. One clear example has been described in the developing spinal cord. Vertebrate lateral motor column (LMC) motoneurons are born in two waves. The first

differentiates into medial LMC neurons that express Isl1 and RALDH-2 (which synthesizes retinoids). Retinoid secretion from those neurons activates expression of Lhx1 in the second wave of LMC neurons, which results in a distinct differentiative outcome [5].

Transcriptional Sub-Programs in Neurons

Neurons often fall into common types, such as motoneurons, neuropeptidergic neurons, ciliated neurons etc. Certain transcription factors independently control the expression of genes that are generic to neurons of a particular type, often in parallel and sometimes in concert with subtype-specific transcription factor codes. In *C.elegans*, DAF-19 is expressed in all ciliated neurons, activating expression of the structural components of ciliary structures independently of subtype-specifying mechanisms. ►Proneural transcription factors are well known to promote cell-cycle exit of progenitors into newborn neurons and activate generic neuronal genes [7]. However, in many cases, these factors are also required to activate cell-specific properties, usually in a context-dependent manner. In the vertebrate spinal cord, Mash1 is essential for the emergence of a subset of dorsal interneurons and Ngn2 for motoneurons. Although both have been shown to act as proneural factors that activate generic neuronal properties in both sets of neurons, they cannot compensate for one another in the subtype-specification of their respective neuronal populations [7]. These date indicate that these factors play at least two distinct roles in the differentiation of their respective neurons, one generic and the other subtype-specific. Work in *Drosophila* has provided direct evidence to demonstrate this duality in function [10]. The bHLH factor *dimmed* is expressed in neuropeptidergic neurons, activating generic genes independently of other transcription factors, but acting combinatorialy with local subtype-specific combinations of transcription factors to activate subtype-specific genes appropriate to the neuropeptidergic cell-type, eg specific neuropeptides [10].

Not only can individual transcription factors act in parallel to cell-specific combinatorial codes to specify generic sets of genes, but certain combinations of transcription factors can operate in this manner as a sub-code in otherwise distinct neurons. These function to turn on the same genes in different neurons [7]. A transcription factor code of Mash1 and Phox2a/b specifies the expression of noradrenalin-synthesizing enzymes in different types of vertebrate neurons. This pro-adrenergic code appears to exist as a sub-code within an otherwise distinct transcription factor milieu to specify this particular aspect of neuronal differentiation [7].

Summary

Our understanding of how combinatorial codes of transcription factors drive diverse programs of neuronal differentiation has progressed dramatically, facilitated by the remarkable conservation of transcription factor function between ►metazoans. The future promises a highly detailed description of the gene regulatory networks that guide the differentiation and maturation of the many types of neurons in the nervous system. This information will be of paramount importance to the development of novel therapeutic approaches aimed at tackling the devastating effects of nervous system disorders and trauma.

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Combined Dexamethasone-CRH (Dex-CRH) Suppression Test

Definition

After oral administration of dexamethasone (Dex) the previous night, patients are injected with corticotrophin releasing hormone (CRH) to examine the efficacy of the

feed back loop of the hypothalamic-pituitary-adrenal (HPA) axis. A strong response to CRH after Dex pre-treatment in rodents has been shown to reflect impaired negative feedback at the pituitary level.

►Neuroendocrinology of Multiple Sclerosis

Command Neuron

Definition

A neuron that can activate a specific behavior or behavioral sequence. There has been a considerable debate concerning the criteria that define a command neuron. The most stringent definition is a neuron, which is both sufficient and necessary for the initiation of a specific behavior. However, whilst many neurons fulfil the sufficiency criterion, i.e. their activity can activate a specific behavior, only very few neurons also fulfil the necessity criterion, i.e. the specific behavior will only be elicited when this neuron is active. This is consistent with the recognition that most behaviors are activated by multiple parallel pathways.

►Central Pattern Generator

Command Nucleus

Definition

A group of neurons that together is both necessary and sufficient for generating a behavior. In the case of mormyrid electric fish, the nucleus is responsible for generating each electric organ discharge (EOD).

►Reafferent Control in Electric Communication

Commissure

Definition

A commissure (Latin joining together) is a bundle of axons that crosses the midline, usually connecting homotypical (the same) cell groups on the left and right sides of the neuraxis, e.g., the corpus callosum, and anterior and posterior commissures. On the other hand, the anterior commissure of the spinal cord is composed of axons from the dorsal horn simply crossing the midline en route to the opposite anterolateral quadrant of the spinal cord white matter.

Common Crus

Definition

Common "leg" (Latin), a portion of the semicircular canal system shared by two canals.

►Evolution of the Vestibular System

Common Marmoset (Callithrix Jacchus)

Definition

Common marmoset are small monkeys (300–500 g at maturity) of Brazilian origin, with a chromosome number of 2n = 46 and a life span of 12–15 years. They are easier to manipulate than Macaque monkeys, and their high breeding efficiency allows an adequate number of common marmosets to be obtained for use in research experiments. Thus, they are often used in a variety of fields of research for preclinical trials, e.g., the experimental autoimmune encephalomyelitis (EAE) model for multiple sclerosis, cerebrovascular disease, Alzheimer's disease, delayed dyskinesia, Parkinsonism, and Huntington's disease.

►Alzheimer's Disease
►Experimental Autoimmune Encephalomyelitis (EAE)
►Huntington's Disease
►Multiple Sclerosis
►Parkinson Disease

Common Sense Functionalism (Folk Functionalism)

Definition

The claim that mental states like beliefs, desires and intentions are understood solely in terms of their causal

relations to other states, to input from the environment and to observable behavior.

►Theory Theory (Simulation Theory, Theory of Mind)

Comparator in Motor Control

Definition

In an engineering model of a feedback system the element that serves as a junction for the input signal and the feedback signal is called a comparator. Since the feedback signal is usually negative and the input signal positive, the comparator computes the difference between the two signals. In neural models, a comparator is hypothesized to compute remaining motor error, the difference between the signal representing the goal of the movement and a feedback signal representing how far the movement has moved toward the goal at the present instant.

Compartmental Approach

Definition

An advanced biophysical model of a single neuron, in which the neuron is represented as a set of electrically coupled isopotential compartments.

►Neural Networks

Compartmentalized Protein Synthesis

►mRNA Targeting: Growth Cone Guidance

Compatibilism

Definition

The thesis that acting freely is compatible with the truth of determinism

►Freedom of Will

Compensatory Linear Vestibulo-Ocular Reflex (lVOR)

Definition

The reflex that responds to high frequency linear accelerations of the head in space to produce eye movements that tend to maintain a gaze point fixed relative to the head. This reflex has been also referred to as the translational VOR (TVOR).

►Velocity Storage
►VOR-translational

Compensatory Plasticity

Definition

Neuronal plasticity to compensate for impaired functionality after injury or experimentally induced lesion (e.g., denervation) (to be distinguished from learning-induced and developmental plasticity).

►Neuroethological Aspects of Learning

Competitive Antagonist

Definition

A competitive antagonist is a receptor antagonist that binds to a receptor but fails to activate it. If an agonist competes with a competitive antagonist for the same binding site on the same receptor, the agonist molecules can be displaced from the binding site.

Competitive Learning

Definition

A learning mechanism of neural networks in which neurons are competing with each other to output maximum value to input signals. As a result of the competition, the input signal space is divided and each neuron becomes to output maximum value for input signals in a certain divided area of signal space.

►Competitive Learning Theory

Competitive Learning Theory

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Definition

►Competitive learning theory refers to mathematical and computational theories on learning of neurons which compete with each other to generate maximum output. Various self-organizing phenomena in the central nervous system such as formation of the feature extraction neurons in the visual cortex are explained by these theories. The theories also explain self-organizing phenomena in cognitive level such as categorization of input stimuli and feature extraction for pattern recognition.

Description of the Theory

Self-Organization of Neural Circuit

Various organized structures are observed in the central nervous system. For example, as Hubel and Wiesel discovered, simple cells which respond selectively to specific visual stimuli such as oriented light bar form aligned columns in the visual cortex, and neurons in neighboring columns respond to similar orientation. Such organized structures composed of neurons which selectively respond to certain stimulus are observed quite often in the nervous system. It is a natural and interesting question how they are constructed. The competitive learning theory is one of major theories to explain the self-organization process of the structures.

Competitive Learning

Consider a set of M neurons. As shown in Fig. 1, all neurons receive the same N input signals $x_1,\ldots, x_N$ from other neurons. Let the synaptic weight of the ith neuron at time t be $\boldsymbol{w}_i(t) = (w_{i1}(t), \ldots, w_{iN}(t))$, $i = 1, \ldots M$. Each discrete time step, input signals $\boldsymbol{x}(t) = (x_1(t), \ldots, x_N(t))$ is fed into the neurons. The output of the ith neuron is assumed to be the weighted sum of inputs, that is, inner product of the vector $\boldsymbol{w}_i(t)$ and $\boldsymbol{x}(t)$,

$$y_i(t) = \sum_{j=1}^{N} w_{ij}(t)x_j(t) = \mathbf{w}_i(t) \cdot \mathbf{x}(t).$$

The neuron which outputs the maximum value is called "winner," and we assume that the synaptic weights of the winner neuron are modified according to the following learning rule:

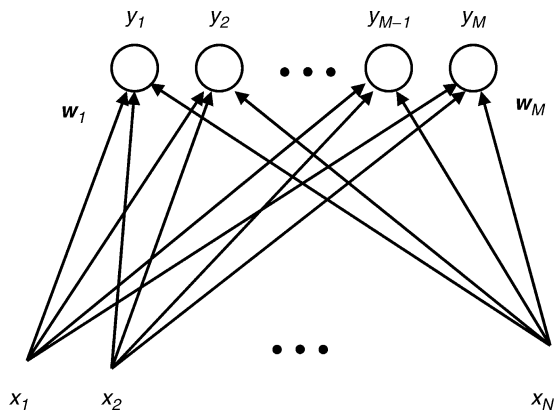
$$\mathbf{w}_i(t+1) = \mathbf{w}_i(t) + \eta(t)(\mathbf{x}(t) - \mathbf{w}_i(t)).$$

Here $\eta(t)$ is a small positive value called learning rate and decreases as time t passed. This rule is the most typical one, and various learning rules are proposed and investigated by many researchers.

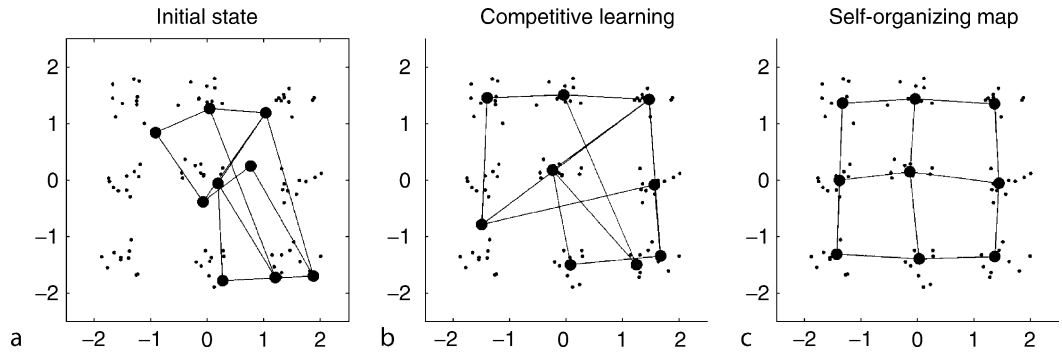
This learning rule causes the weight vector of the winner to become closer to the input signal vector. If the several input signals form a cluster, then the weight vector comes closer to the center of the cluster. Figure 2 illustrates the result of the competitive learning. Here $M = 9$ and $N = 2$, and nine neurons are arranged on a 3×3 two dimensional grid. Input signals and weight vectors are shown by small and large dots respectively. The weight vectors of neighboring neurons are connected by a line. Input signals are distributed forming nine clusters. At the initial state shown in Fig. 2a, nine weight vectors $\boldsymbol{w}_i$ are distributed randomly. Hence, a weight vector is closest to a certain cluster. For the input signal in the closest cluster, the neuron which has the weight vector will become the winner and the weight vector comes closer to the cluster center. In the end, each weight vector goes to the center of a cluster as is shown in Fig. 2b.

In this way, competitive learning neurons can find clusters in the input signal space, and each neuron becomes to output maximum response to signals in a cluster. This means that the neuron becomes a detector of the cluster. Imagine that each input signal is a light bar stimuli in some orientation, then the competitive learning can produce the orientation selective neurons.

Choosing the winner neuron and applying the learning rule only to it may seem an artificial trick. However, various biologically plausible neural network architectures, which can realize the equivalent process, have been proposed. Most of them are composed of Hebbian learning neurons and mutual inhibition between neurons.



Competitive Learning Theory. Figure 1 A competitive learning network.



Competitive Learning Theory. Figure 2 Competitive learning and self-organizing map.

An important factor for the success of the competitive learning is the number of learning neurons. If the number is smaller than the number of clusters, the result of learning will not be stable. However, it is impossible to know the number of clusters beforehand. Taking the dynamic nature of learning environments into consideration, the problem becomes more serious. Even though the number of output cells is enough at a certain time, there is a possibility that new clusters will emerge according to the change of the environment. In order to cope with the problem, Grossberg first proposed an idea to add output units one by one during the learning process and called it adaptive resonance theory [1]. This idea of adding or removing output units during learning was further investigated by many researchers and various heuristic rules for addition or deletion were proposed.

From a computational or engineering point of view, the competitive learning solves the problem called clustering, categorization, or vector quantization. The procedure of the competitive learning is closely related to clustering algorithms such as the k-means algorithm and the ►expectation maximization learning of Gaussian mixture distribution. The idea of the competitive learning was extended to competition between modular neural circuits. Jacobs et al. proposed a learning model named "mixture of experts," where multiple modular networks are competing and each network becomes an expert for a certain subtask [2]. Haruno et al. also proposed a model of self-organization of functional modules and named it "Mosaic." They applied the model to the problem of complex motor learning [3].

Formation of Cortical Maps

The competitive learning explains formation of neurons which respond to specific input signals selectively. In cortical maps, it is known that such feature detecting neurons are arranged as the neighboring neurons tend to respond to similar inputs. The self-organizing maps (SOM) proposed by Kohonen is one of the most popular mathematical models of the formation of the cortical maps [4]. Kohonen proposed to apply the learning procedure not only to the winner neuron but also the neurons close to the winner. A typical learning rule can be written as

$$\mathbf{w}(t+1) = \mathbf{w}(t) + \eta(t)\, D(i, i^*, t)(\mathbf{x}(t) - \mathbf{w}(t)).$$

Here, $D(i,i^*,t)$ is called neighborhood function and takes 1 for neuron i close to the winner neuron i*. The learning rate $\eta(t)$ and the neighboring area where $D(i,i^*,t) = 1$ are controlled to become smaller as the learning proceeds. Various modifications of the learning rule have been proposed and investigated by many researchers.

Figure 2c shows the result of the self-organizing process. The initial state and the input signals are the same as the competitive learning. Note that the lines connecting neighboring neurons are resolved and neighboring neurons begin to respond to neighboring clusters.

In order to realize the neighborhood function in a biologically plausible way, various network architectures have been proposed. Most of them are composed of excitatory connections between neighboring neurons and inhibitory connections between far away neurons. Due to the connections, neighboring neurons begin to behave similarly and separated neurons begin to behave competitively.

Models of the Development of the Visual Cortex

We have introduced two elements of self-organization mechanism. The first one is the competition between neurons for generating selectively responding neurons. The second one is the positive interaction within the neighborhood for generating a topology preserving arrangement of neurons. A mathematical model of the self-organization process of orientation sensitive cells in the visual cortex, which has the above two elements, was first proposed by von der Malsburg [5]. The model

is composed of two layers of excitatory neurons and inhibitory neurons connecting each other. Using the set of orientating light bar as stimuli, the model succeeded to produce the orientation sensitive cells through the learning. The neighboring cells had the tendency to react to similar stimuli as discovered by Hubel and Wiesel.

Inspired by the work, many researchers proposed and studied various versions of models. Amari performed deep mathematical analysis of the model, and theoretically proved important natures of the model such as the formation of discrete column structures and the stability of the organized structure [6]. Linsker proposed a multilayer network of Hebbian learning neurons [7]. Instead of competition between neurons in a layer, localization of connections between layers was introduced, that is, each neuron receives inputs only from a neighborhood in the previous layer. It was demonstrated by computer simulation that featured extraction cells such as on-center off-surround type cells, and orientation sensitive cells that emerged in the higher level layers. The most interesting point of this model is that the input signal is just a white noise without any structure. Hence, this model can explain the fact that even in the visual cortex of very young animals which have no visual stimulus, some orientation specific cells are found. Miller et al. improved Linsker's model to be more biologically realistic [8]. Tanaka proposed more sophisticated mathematical models using the formalism of the statistical mechanics and succeeded in reproducing a very natural pattern of occular dominance columns and orientation columns [9]. Olshausen et al. incorporated the maximum information preservation principle and sparse coding principle, and have shown simple-cell like receptive fields by using natural images as input stimulus [10].

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Complement

Definition

An important innate immune system composed of almost 30 proteins expressed by phagocytes, glial cells, neurons and most other cell types. C3 is the canonical complement protein with the capacity to bind to pathogens and promoting clearance by phagocytes expressing C3 receptors. Small fragments of C3 called C3a and C5a anaphylatoxins have stimulatory activities through signaling to G-protein-coupled seven transmembrane receptors.

Complement System

Definition

It is a cascade of more than 30 proteins in the plasma, and forms an important part of the host immune system and normal inflammatory response. Under normal circumstances, the activation of the complement components is controlled by complement regulatory proteins. However, the system is up-regulated in many disorders of the brain. The major pathways of complement activation are the classical pathway (CP), the alternative pathway (AP) and the Lectin pathway. Although, controlled activation of the complement system is beneficial and neuroprotective, the uncontrolled activation leads to neurodegeneration.

►Central Nervous System Disease – Natural Neuroprotective Agents as Therapeutics

Complementary DNA (cDNA)

Definition

A complementary DNA copy of an mRNA synthesized by reverse transcriptase.

Complete Homonymous Hemianopsia

Definition

►Hemianopsia

Completeness of the Physical Domain

Definition

For any physical event p, insofar as p has a cause, it has a complete physical cause.

►Causality

Complex, Basal, of the Amygdala

Definition

The basal (also called basolateral, including rostromedial magnocellular and caudolateral parvocellular divisions), accessory basal (also called basomedial) and lateral nuclei of the amygdala. These nuclei are composed of neurons that much resemble those in the cortex, including a variety of calcium binding proteinimmunoreactive interneurons and pyramidal neurons that are reciprocally connected with other parts of the cortex. In view of these characteristics, the nuclei of the basal complex have been regarded as cortical-like, despite lacking a laminar organization.

►Ventral Striatopallidum

Complex Behavior

►Cognitive Elements in Animal Behavior

Complex Cells in Visual Cortex

Definition

Complex cells are one of two main physiological types of cells in the primary visual cortex. They differ from the other class (simple cells) in that their receptive fields lack segregated On and Off subregions. Complex cells are usually tuned for stimulus orientation and excited by bright or dark contours placed anywhere inside the receptive field.

Unlike simple cells, which are similar to one another in many ways, complex cells have heterogeneous response properties that vary according to cortical layer of origin.

►Form Perception
►Striate Cortex Functions
►Visual Cortical and Subcortical Receptive Fields

Complex Partial Seizures (Temporal-lobe or Psychomotor Seizures)

Definition

These seizures may start with an aura that arises in the ►autonomic, ►visceral and ►olfactory regions of the ►temporal lobe and ►limbic system. The aura is characterized by ►auditory, ►gustatory, olfactory or visual ►hallucinations; by changes in cognition such as déjà vu, jamais vu or recurrent memories; by illusions of spatial distortions, shrinkage or angulation; and by affective alterations (anxiety, fear, seldom rage). The aura may terminate the attack or transcend into movements or behaviors (swallowing, smacking the lips, undressing, ►dysphasic speech), which the patient is ►amnesic of after the attack.

Complex Receptive Fields

Definition

►Visual Cortical and Subcortical Receptive Fields

Complex Regional Pain Syndromes: Pathophysiological Mechanisms

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Definition

►Complex regional pain syndrome (CRPS) type I (previously termed ►reflex sympathetic dystrophy) is

characterized by pain (spontaneous pain, hyperalgesia, and allodynia), active and passive movement disorders, abnormal regulation of blood flow and sweating, edema and trophic changes. It typically develops after trauma with a small or no obvious nerve lesion at an extremity (e.g., bone fracture, sprains, bruises or skin lesions, surgeries); occasionally it may develop after remote trauma in the visceral domain (e.g., myocardial ischemia) or even after a central nervous system (CNS) lesion (e.g., stroke). An important feature of CRPS I, which cannot be overemphasized, is that *the severity of symptoms is disproportionate to the severity of trauma* with a tendency to spread in the affected distal limb. The symptoms are not confined to the innervation zone of an individual nerve. Thus, all symptoms of CRPS I in their typical pattern may occur *irrespective of the type of the preceding lesion*. CRPS Type II (previously termed causalgia) is similar in its symptoms to that of CRPS I, the only exception being that a partial nerve lesion of a peripheral nerve is mandatory for its diagnosis [1–5].

This paper will discuss the underlying mechanisms of CRPS, in particular type I, and focus on the ►sympathetic nervous system. An explanatory ►hypothesis will be presented showing that the syndrome is mainly a systemic disease involving the central nervous system and the peripheral nervous system.

Characteristics

Observations in Human Patients and their Underlying Mechanisms

Somatic Sensory Abnormalities and Pain

Until recently, experimental investigations have mainly concentrated on ►pain, sympathetically maintained pain (SMP) and abnormalities of the skin. This has led to a rather limited view, with a tendency to put the nociceptive system and its peripheral coupling to the sympathetic nervous system into the foreground. Yet clinical observations demonstrate that in CRPS I, pain is commonly projected into the deep somatic tissues, that many patients with CRPS I do not have SMP (as judged by clinical criteria, i.e., the patients have no significant decrease in pain following sympathetic blocks), and that some 5% of the patients with CRPS I do not have spontaneous pain (and rather discrete evoked pathological pains).

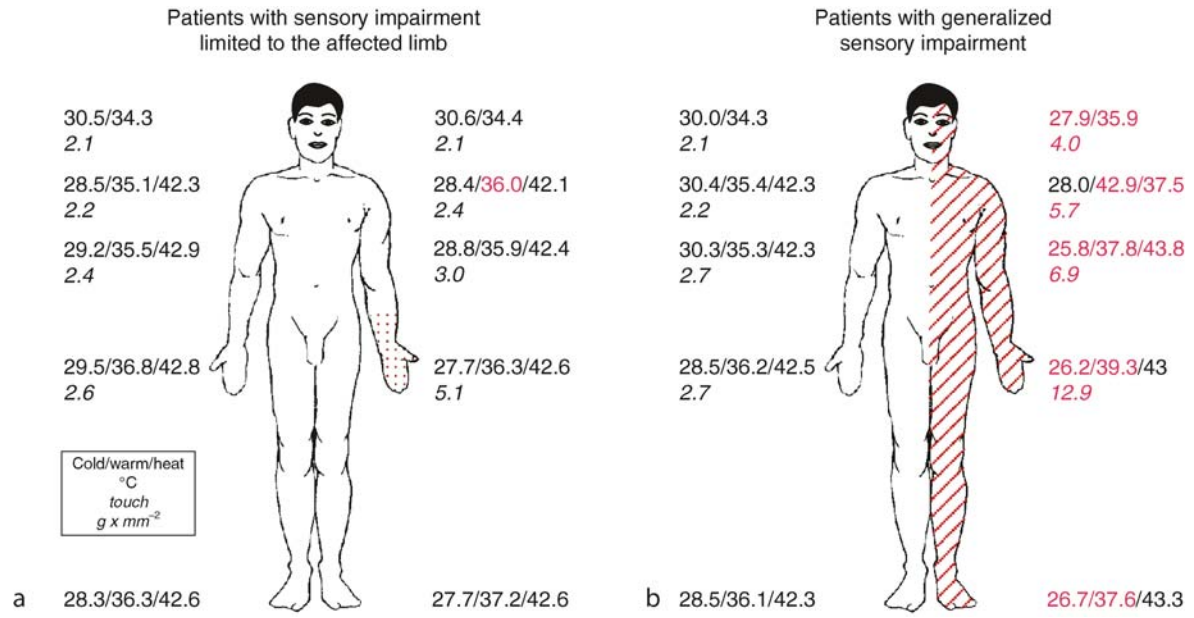
Pain and Other Somatic Sensations

Patients with CRPS I generally report a burning spontaneous pain felt mostly deep in the distal part of the affected extremity. Characteristically, the pain is disproportionate in intensity to the inciting event. Stimulus-evoked pains include mechanical, cold and heat allodynia and/or hyperalgesia. These sensory abnormalities often appear early, are most pronounced distally, and have no consistent spatial relationship to individual nerve territories or to the site of the inciting trauma. Typically, pain can be elicited by movements and pressure at the joints (deep somatic allodynia), even if these are not directly affected by the inciting lesion, indicating that the deep somatic tissues are involved [1]. Based on experimental findings in animals, spontaneous pain and various forms of allodynia/hyperalgesia at the distal extremity are thought to be generated by processes of peripheral and central sensitization.

Fifty per cent of patients with chronic CRPS I develop hypoesthesia and hypoalgesia on the affected half of the body, or in the upper quadrant ipsilateral to the affected extremity. Quantitative sensory testing has shown that these patients have increased thresholds to mechanical, cold, warmth and noxious heat stimuli in the affected part of the body compared with the responses generated from the corresponding contralateral healthy body side (Fig. 1). Patients with these extended sensory deficits have longer illness duration, greater pain intensity, a higher frequency of mechanical allodynia, and a higher tendency to develop changes in the somatomotor system than do patients with spatially restricted sensory deficits [1,2,6]. The anatomical distribution of these changes suggests that they are due to CNS changes, which may cause widespread alterations in the perception of painful as well as non-painful sensations.

These findings have considerable implications:

- The central representation of somatosensory sensations is changed, probably in the thalamus and cortex. This implication is supported by studies on CRPS patients using positron emission tomography (PET) or magnetoencephalography (MEG) [1,2].
- If generalized sensory deficits in patients with chronic CRPS I are permanent and irreversible, it would be the *first* documented case of such irreversible changes in the brain that is triggered by trauma with minor or *no* nerve lesion.
- Most CRPS I patients have deep somatic spontaneous pain and mechanical hyperalgesia/allodynia. Are the non-painful sensations elicited from muscle and joints changed as well?
- Do the generalized sensory changes depend on a continuous nociceptive input from the affected extremity and disappear after successful treatment of the pain? After all, the continuous nociceptive afferent input could be subthreshold for the conscious perception of pain, but high enough to maintain the central changes.
- Are the somatosensory changes (including pain) independent of a continuous nociceptive afferent input, but fully dependent on dynamic changes in the central ►somatosensory system?



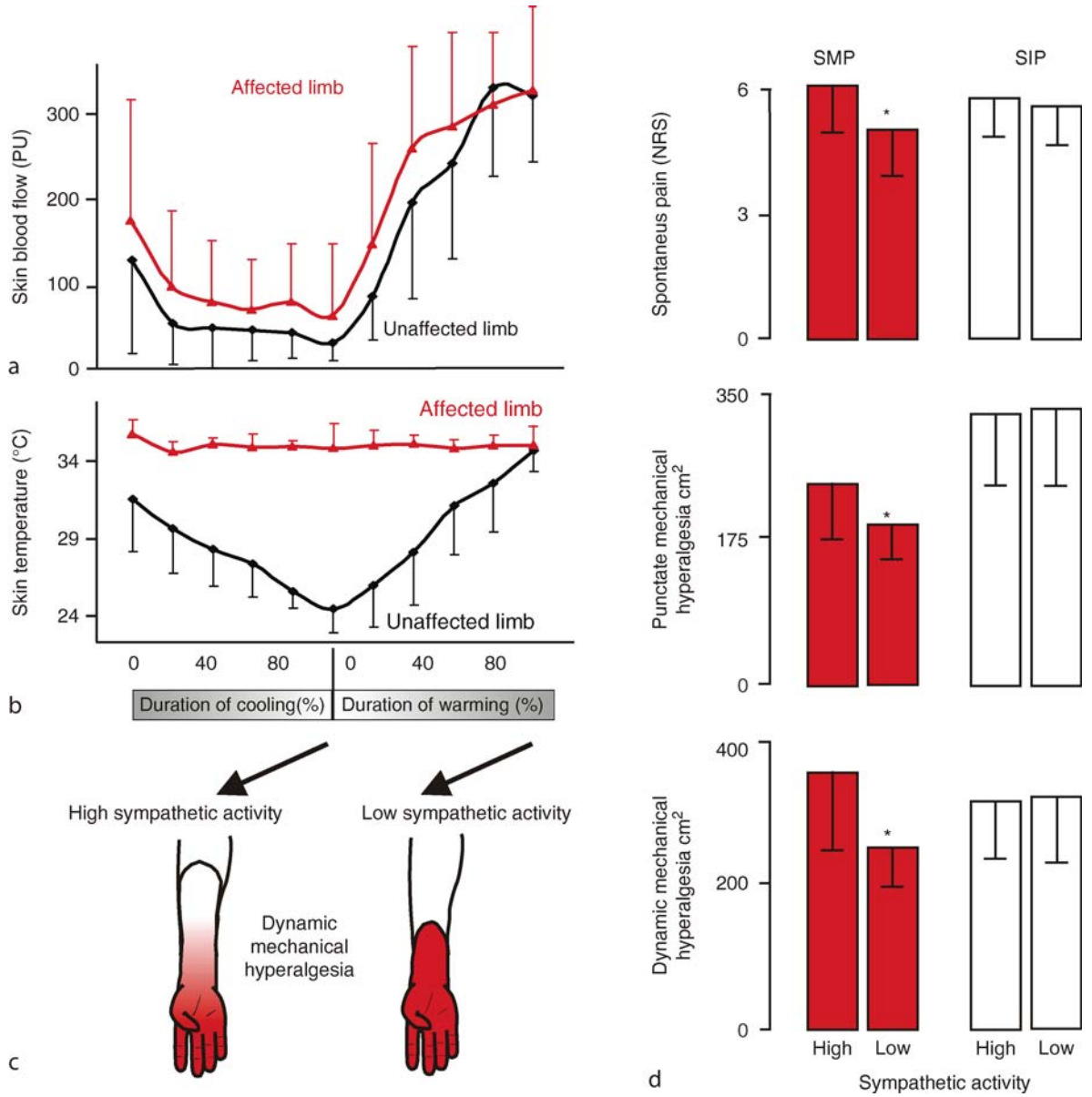
Complex Regional Pain Syndromes: Pathophysiological Mechanisms. Figure 1 Detection thresholds to cold, warm and heat stimuli (*upper rows*) and to von Frey filament stimulation (*lower rows* in italic) in CRPS I patients with sensory impairment spatially restricted to the affected side (a) and in CRPS I patients with generalized sensory impairment (b). The thermal stimuli were applied utilizing the Peltier effect. Cool and warm stimuli were applied at a rate of 0.7°C·s^{-1} on a skin surface of 5.8 cm^2, starting from a reference temperature of 32°C ± 0.5°C. Heat stimuli were applied at the same rate and surface, but starting from a reference temperature of 40°C. Detection threshold to von Frey filament stimulation in g·mm^{-2}. Cooling and warm stimuli applied to face, chest, upper arm, hand and foot (N = 14 patients). Heat stimuli applied to chest, upper arm, hand and foot (N = 14 patients). Mechanical stimuli with von Frey filaments applied to face, chest, upper arm/thigh and hand/foot (N = 24 to 25 patients with limited sensory impairment; N = 15 patients with generalized sensory impairment). Generalized sensory changes occur preferentially in chronic CRPS I patients, and are correlated with a higher incidence of mechanical allodynia and motor deficits than in CRPS I with spatially restricted sensory changes. Numbers show mean values. Significant differences between left and right are indicated in red (two-tailed paired *t*-test, $p < 0.05$). Modified from Rommel O, Malin JP, Zenz M, Jänig W (2001) Pain 93:279–293.

Sympathetically Maintained Pain (SMP)

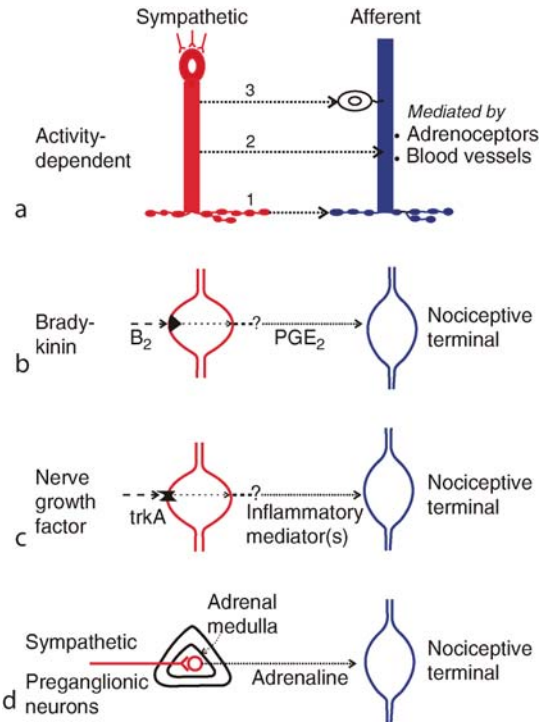
Influence of Sympathetic Activity and Catecholamine on Primary Afferents in Patients with CRPS

Clinical studies in humans support the idea that cutaneous nociceptors may develop catecholamine sensitivity after partial nerve lesions (CRPS II). Intracutaneous application of noradrenaline into a symptomatic skin area may rekindle spontaneous pain and dynamic mechanical hyperalgesia/allodynia that had been relieved by sympathetic blockade [6–8]. Intracutaneous injection of noradrenaline in control subjects does not elicit pain.

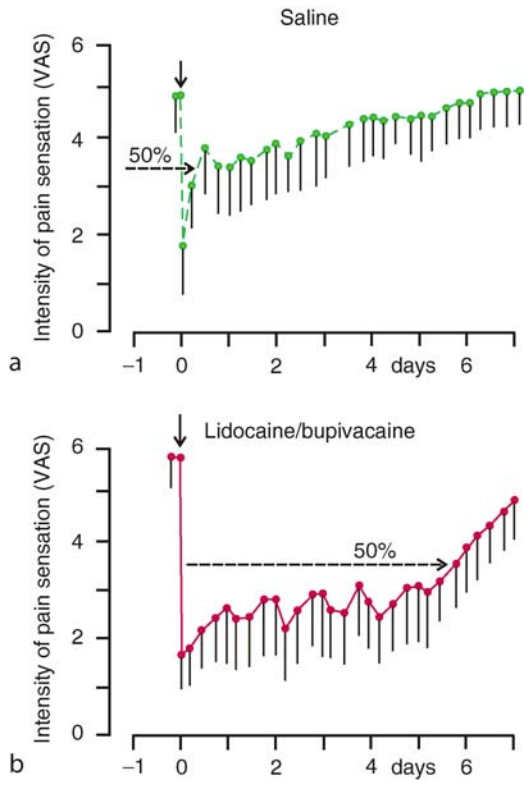
In CRPS I patients with SMP, selective activation of the cutaneous sympathetic vasoconstrictor outflow to the painful extremity by whole body cooling increases the intensity of spontaneous pain and mechanical hyperalgesia/allodynia (dynamic/punctate), and the area of dynamic mechanical hyperalgesia/allodynia, but not in CRPS I patients without SMP (Fig. 2). In these CRPS patients with SMP, the relief of spontaneous and evoked pain after sympathetic blockade is significantly more pronounced than the changes in spontaneous and evoked pain induced experimentally by sympathetic activation, which is generated experimentally by change of the activity in cutaneous vasoconstrictor neurons from the thermoregulatory hot state (cutaneous vasoconstrictor activity absent or low) to the thermoregulatory cold state (cutaneous vasoconstrictor activity high) (44.0% ± 9.1% vs. 16.0% ± 4.0%, $p < 0.05$ [1,2]). This difference in reduction of pain is explained by the fact that a complete sympathetic block affects *all* sympathetic outflow channels projecting to the affected extremity. Thus, sympathetic-afferent coupling may particularly occur in the deep somatic domain such as bone, muscle or joint, and less so in the skin. That the deep somatic structures are especially extremely painful in some cases with CRPS supports this view [1,2].



Complex Regional Pain Syndromes: Pathophysiological Mechanisms. Figure 2 Experimental modulation of cutaneous sympathetic vasoconstrictor neurons by physiological thermoregulatory reflex stimuli in 13 CRPS patients. With the help of a thermal suit, whole-body cooling and warming was performed to alter sympathetic skin nerve activity. The subjects were lying in a suit supplied by tubes, in which running water of 12°C and 50°C, respectively (inflow temperature) was used to cool or warm the whole body. By these means sympathetic activity can be switched on and off. (a) High sympathetic vasoconstrictor activity during cooling induces considerable drop in skin blood flow on the affected and unaffected extremity (laser Doppler flowmetry). Measurements were taken at 5 min intervals (mean + SD). (b) On the unaffected side, a secondary decrease of skin temperature was documented. On the affected side, the forearm temperature was clamped at 35°C by a feed-back-controlled heat lamp to exclude temperature effects on the sensory receptor level. Measurements were taken at 5 min intervals (mean + SD). (c) Effect of cutaneous sympathetic vasoconstrictor activity on dynamic mechanical hyperalgesia in one CRPS patient with sympathetically maintained pain (SMP). Activation of sympathetic neurons (during cooling) leads to an increase of the area of dynamic mechanical hyperalgesia. (d) Spontaneous pain (*upper*; NRS, numerical rating scale), area of punctuate mechanical hyperalgesia (*middle*; in cm^2) and area of dynamic mechanical hyperalgesia (*lower*; in cm^2) during high sympathetic activity to the skin (whole body cooling) or low sympathetic activity to skin (whole body warming) in CRPS I patients with sympathetically maintained pain (SMP, N = 7) and CRPS I patients without SMP (sympathetically independent pain [SIP], N = 6). Mean + 1 SD. *, $p < 0.05$ (Wilcoxon's paired test). Modified from Baron R, Schattschneider J, Binder A, Siebrecht D, Wasner G (2002) Lancet 359:1655–1660.



Complex Regional Pain Syndromes: Pathophysiological Mechanisms.
Figure 3 (a) Possible ways of coupling between sympathetic neurons and primary afferent neurons following peripheral nerve lesion. These types of coupling depend on the activity in the sympathetic neurons and on the expression of functional adrenoceptors by the afferent neurons or are mediated indirectly via the blood vessels (blood flow). It can occur in the periphery (1), in the dorsal root ganglion (3) or possibly also in the lesioned nerve (2). (b–d) Ways of coupling between sympathetic neurons and nociceptive afferent neurons which are possibly not dependent on activity in the sympathetic neurons (b, c′) or involve the sympatho-adrenal system (d). (b) The inflammatory mediator bradykinin (BK) reacts with B2 receptors in the membrane of the sympathetic varicosities, inducing release of prostaglandin E_2 (PGE_2) and sensitization of nociceptors. (c′) Nerve growth factor (NGF) released during an experimental inflammation reacts with the high-affinity receptor trkA and/or the low-affinity panneurotrophin receptor p75 for NGF in the membrane of the sympathetic varicosities, inducing release of an inflammatory mediator or inflammatory mediators and sensitization of nociceptors. (d) Activation of the adrenal medulla by sympathetic preganglionic neurons leads to release of a hormone (possibly adrenaline) which generates sensitization of nociceptors. For details and literature see text and [8,10]. Modified from Jänig W, Häbler HJ (2000) Prog Brain Res 129:451–468.



Complex Regional Pain Syndromes: Pathophysiological Mechanisms. Figure 4 Affect of sympathetic blocks with a local anesthetic (lidocaine/bupivacaine) or of injection of saline close to the corresponding paravertebral sympathetic ganglia on pain in seven patients with CRPS I.Double-blind crossover study. Effect on pain following both interventions at the sympathetic supply was measured in the *same* group of CRPS I patients. Pain was systematically measured repeatedly using the visual analogue scale (VAS) on the day of the injection and on seven days after the injection. Both interventions produced pain relief (see 50% value of pain relief). However, the mean relief of pain to injection of the local anesthetic lasted for 6 days, and was significantly longer than the mean pain relief following local injection of saline, which lasted for 6 h (placebo block). The initial maximal peaks of analgesia were not statistically different. Means + SEM. Modified from Price DD, Long S, Wilsey B, Rafii A (1998) Clin J Pain 14:216–226.

Mechanisms involved in SMP

Quantitative measurements in patients with CRPS I with SMP clearly demonstrate: (i) that the underlying mechanism of SMP must be a coupling between sympathetic noradrenergic neurons and primary afferent neurons in the periphery of the body, and (ii) that the mechanism of this coupling is different in CRPS II compared to that in CRPS I.

Animal models support the peripheral mechanisms of SMP occurring in CRPS II (Fig. 3a; for review [7, 8]). Coupling of sympathetic neurons not only to nociceptive afferent neurons but also to non-nociceptive mechanosensitive or cold-sensitive neurons may turn out to be important. Sympathetic activation of these afferent

neurons may excite sensitized or hyperexcitable central neurons of the somatosensory system (e.g., in the dorsal horn) and contribute to mechanical or cold allodynia in CRPS II patients.

It is unlikely that mechanisms of SMP occurring in CRPS II (i.e., after trauma with nerve lesion) can explain SMP in CRPS I. In CRPS I patients with SMP, only a minor component of the coupling occurs in the skin (see above). It is suggested that an important sympathetic-afferent coupling occurs in the deep somatic tissues [9], and that the mechanism of this coupling is indirect, involving the vascular bed and possibly other non-neural components. This mode of coupling, although repeatedly postulated, has never been explored experimentally using animal models.

Other potential ways of coupling between sympathetic neurons and afferent nociceptive neurons have been developed from animal experiments, but have not been explored in patients (Fig. 3b). These modes of coupling do not involve activity in the sympathetic nerve fibers, but the sympathetic fibers may mediate the effects of inflammatory mediators (e.g., bradykinin) or other compounds (e.g., nerve growth factor) to nociceptive fibers in the peripheral tissue. This sympathetic-afferent coupling may turn out to be important in inflammatory pain and in CRPS I [7,8,10].

Finally, the sympathetic nervous system may be involved in coupling to nociceptive neurons via the adrenal medulla (Fig. 3b). Behavioral experiments have shown this mechanism to exist in rats, implying that adrenaline released by the adrenal medulla (during its activation by preganglionic neurons) leads to sensitization of nociceptors for mechanical stimulation. The process of sensitization has a slow time course, taking up to 2 weeks to fully develop [7,8,10].

The Pain-Relieving Effect of Sympathetic Blocks

In CRPS patients with SMP, pain relief outlasts the conduction block of sympathetic neurons by at least one order of magnitude. Sometimes only a few temporary sympathetic blocks (and in the extreme only a single block) are necessary to produce permanent pain relief (Fig. 4). The long-lasting pain-relieving effects of sympathetic blocks clearly argue that activity in sympathetic neurons, which is of central origin, maintains a positive feedback circuit via the primary afferent neurons. Animal models for positive feedback circuits are lacking. It is postulated that activity in sympathetic neurons maintains a central state of hyperexcitability (e.g., of neurons in the spinal dorsal horn), via excitation of afferent neurons initiated by an intense noxious event. The persistent afferent activity necessary to maintain such a central state of hyperexcitability is probably low. This central state of hyperexcitability is switched off during a temporary block of conduction in the sympathetic chain lasting only a few hours. It cannot be switched back on when the block wears off and the sympathetic activity returns, along with the sympathetically-induced activity in afferent neurons. Sympathetic systems and afferent systems innervating deep somatic tissues may be more important than those innervating the skin in this hypothetical positive feedback circuit, and they need to be investigated experimentally [1,2].

Sympathetic Systems and Regulation of Target Organs in Skin and Deep Somatic Tissues

In CRPS, abnormalities related to the sympathetic nervous system include changes of sweating and skin blood flow [1,2]. In the acute stages of CRPS I, the affected limb is more often warmer than the contralateral limb. Sweating abnormalities, either hypohidrosis or, frequently in acute stages, hyperhidrosis, are present in almost all CRPS I patients [1].

Sympathetic denervation and mechanisms of denervation hypersensitivity cannot account for vasomotor and sudomotor abnormalities in CRPS I patients, since there is no overt nerve lesion [1,2]. In fact, there is direct evidence for a reorganization of central autonomic control in these syndromes. Resting sweat output is increased in many CRPS I patients, as is thermoregulatory and axon reflex sweating. Increased sweat production cannot be explained by a peripheral mechanism since, unlike blood vessels, sweat glands do not develop denervation supersensitivity.

Studies of central reflexes in the cutaneous vasoconstrictor innervation induced by thermoregulatory (whole-body warming or cooling) and respiratory stimuli (by measuring skin temperature and skin blood flow bilaterally at the extremities using infrared thermometry and laser Doppler flowmetry) demonstrate changed vascular regulation patterns in CRPS I patients [1,2]: (i) In the acute stage (<6 months) the affected limb is warmer and skin perfusion values are higher than contralaterally. Body cooling or respiratory stimuli (deep inspiration and expiration) fail to activate cutaneous vasoconstrictor neurons. Noradrenaline levels from the venous effluent from the area of pain are reduced in the affected extremity. (ii) In the chronic stage, temperature and perfusion are lower, and noradrenaline levels are still decreased on the affected side.

The changes in thermoregulatory and respiration-related sympathetic reflex activity in *acute CRPS I*, as reflected by changes of cutaneous blood flow and temperature, can only be attributed to central changes of the cutaneous vasoconstrictor system. These central changes are fully reversible after successful treatment of CRPS. Secondary changes of neurovascular transmission, which are reflected in supersensitivity of the vascular smooth muscle as a consequence of chronically decreased activity in the vasoconstrictor neurons, may account for the severe vasoconstriction and cold skin in *chronic CRPS I* [1,2]. Thus, the decreased levels

of noradrenaline are fully consistent with the cutaneous vasoconstriction observed.

Based on the observation that the changes in patients are restricted to the affected side and are not present on the contralateral extremity, it is postulated that these changes occur in the spinal autonomic circuits. Thus, descending systems, which normally mediate signals to these spinal autonomic circuits from supraspinal centers being involved in thermoregulation (e.g., in hypothalamus and brain stem), may no longer have access to these spinal autonomic circuits, which are linked to peripheral cutaneous vasoconstrictor pathways. By the same token, this may explain the dysregulation of sweat glands. In support of this idea, animal experiments have demonstrated that experimental nerve lesions lead to chronic changes, sometimes persisting for several years, in chemoreceptor, baroreceptor, and nociceptor reflexes in cutaneous vasoconstrictor neurons, but not in muscle vasoconstrictor neurons. The differentiation in reflex pattern between muscle and cutaneous vasoconstrictor neurons disappears, and cutaneous vasoconstrictor neurons tend to exhibit reflexes that are identical to those of muscle vasoconstrictor neurons [4,6]. However, there is no animal model simulating the changed reflex pattern in cutaneous sympathetic neurons in CRPS I.

Somatomotor System

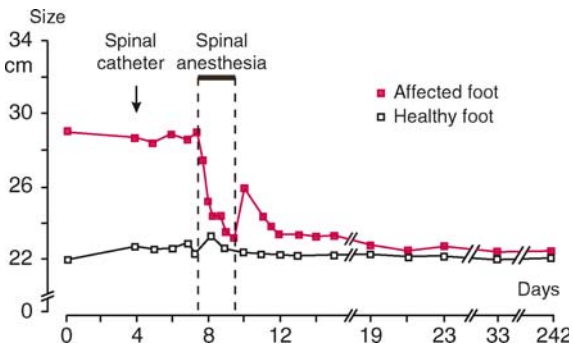
About 50% of CRPS patients show a weakness of all muscles of the affected distal extremity and a decrease of active range of motion. Small precise movements are characteristically impaired. About half of the patients have a postural or action tremor that represents an increased amplitude of physiological tremor. In about 10% of cases, dystonia of the affected hand or foot develops, especially in chronic cases. Furthermore, a neglect-like syndrome is clinically described to be responsible for the disuse of the extremity.

The motor changes are unlikely to be related to a peripheral process (e.g., influence of sympathetic nervous system on neuromuscular transmission or on the contractility of skeletal muscle). Since these changes are lateralized, they may be related to changes in spinal reflex circuits linked to the motoneurons, i.e., they have a central origin. They may be induced by the continuous nociceptive input. However, it is entirely unclear why these motor changes may disappear after sympathetic blocks in CRPS patients with SMP. Animal models to study these motor changes systematically do not exist and have to be developed.

A pathological sensorimotor integration located in the parietal cortex may induce an abnormal central programming and processing of motor tasks. A recent controlled study also supports the view of a mismatch between central motor output and sensory input as an underlying mechanism in CRPS. Using the method of mirror visual feedback, it was shown that the visual input from a moving unaffected limb to the brain is able to re-establish the pain-free relationship between sensory feedback and motor execution. After six weeks of therapy, pain and function were improved as compared with the control group [1–3].

Inflammation and Edema: Role of the Sympathetic Nervous System

Controversial issues are the mechanisms underlying swelling (edema) and inflammation in CRPS (in particular CRPS I). *Swelling* is a very common symptom in acute CRPS patients, and mostly extends far beyond the territory of the trauma. It depends very critically on aggravating stimuli and may decrease following sympathetic blocks, indicating that activity in sympathetic neurons is important in maintaining it (Fig. 5). However,



Complex Regional Pain Syndromes: Pathophysiological Mechanisms. Figure 5 Spinal anesthesia reduced severe edema in a patient with CRPS I. Female patient, 15 years, 3 months after trauma on foot. No spontaneous pain, cutaneous hyperalgesia or allodynia, but deep hyperalgesia. Implantation of spinal catheter at thoracic level T10 on day 4. Spinal anesthesia for 43 h starting on day 7 with 1.4 ml 0.5% bupivacaine per hour. Increase in skin temperature of foot to 36°C (indicating complete decrease of activity in cutaneous vasoconstrictor neurons). Significant decrease of edema in 1 day and its complete disappearance with time after termination of the spinal anesthesia together with the other symptoms of CRPS I. The decrease of the edema was considered to be due to decrease of activity in sympathetic neurons. However, the following possibility cannot entirely be excluded: Peptidergic primary afferent neurons with unmyelinated fibers may conduct impulses antidromically to the periphery and generate the swelling. These antidromic impulses are produced by continuous strong primary afferent depolarization of the central terminals of these afferent neurons (Willis WD (1999) Exp Brain Res 124:395–421). Spinal anesthesia interrupts the primary afferent depolarization. Modified from Blumberg H, Hoffmann U, Mohadjer M, Scheremet R (1994) In: Gebhart GF et al. (1994) Prog in Pain Res and Management, vol 22, IASP, Seattle.

the underlying mechanism is entirely unknown. It is important to emphasize that one block or a few blocks of sympathetic activity may lead to a long-lasting (sometimes permanent) decrease of edema, this being reminiscent of the long-lasting decrease of pain following sympathetic blocks in CRPS patients with SMP (Fig. 4).

- It has been proposed that the capillary filtration pressure is high due to an imbalance of the activity or pattern of activity between vasoconstrictor neurons innervating precapillary blood vessels and those innervating postcapillary blood vessels (e.g., veins). Accordingly, venous congestion plethysmography shows that the hydrostatic pressure to achieve net capillary filtration is elevated on the affected side in patients with CRPS [1,2]. However, venules and small deep veins are not, or only sparsely, innervated by sympathetic noradrenergic fibers, if at all. Thus, the sympathetic fibers do not form close contacts with the smooth muscle cells of the venules as they do with the precapillary resistance vessels (Fig. 6a).
- Sympathetic fibers may be coupled to peptidergic unmyelinated fibers leading to release of peptides with subsequent precapillary vasodilation and postcapillary (venular) plasma extravasation (neurogenic inflammation) (Fig. 6a). However, animal models supporting this idea are lacking.

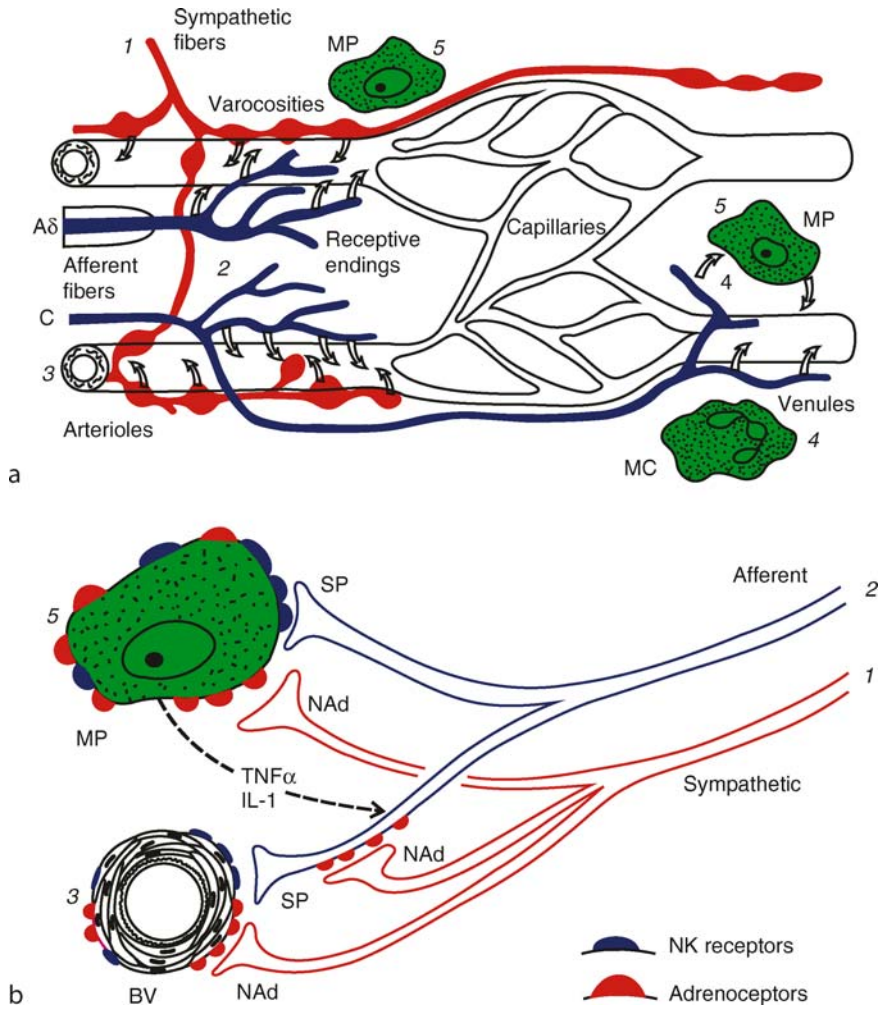
The idea that CRPS I patients undergo *inflammatory processes* in the affected extremity, in particular in the deep somatic tissues including bones, goes back to Sudeck who believed that this syndrome is an inflammatory bone atrophy [6]. Accordingly, bone scintigraphy has demonstrated periarticular tracer up-take in acute CRPS and synovia biopsies, and scintigraphic investigations with radiolabeled immunoglobulins have shown protein extravasation, hypervascularity and neutrophil infiltration. Microdialysis through the skin revealed that evoked neurogenic inflammation produced by activation of peptidergic unmyelinated afferents is enhanced, and that lactate is increased in the skin, suggesting enhanced anaerobic glycolysis due to tissue hypoxia. In the fluid of artificially produced skin blisters of the involved extremity, significantly higher levels of interleukin 6 (IL-6) and tumor necrosis factor α (TNF α) are present. Furthermore, based on animal experiments, it is proposed that oxygen-derived free radicals are involved, leading to an increase in vascular permeability, soft tissue damage and pain (for references [1,6]).

Although there is some evidence that inflammatory processes are involved in the pathogenesis of early CRPS, the exact mechanisms of initiation and maintenance of these reactions are still unclear. Animal studies demonstrate that the sympathetic nervous system can influence the intensity of an inflammatory process [7,8], and clinical studies indicate that sympatholytic procedures can ameliorate both inflammation and edema in humans. However, this concept has yet to be proven in patients with CRPS.

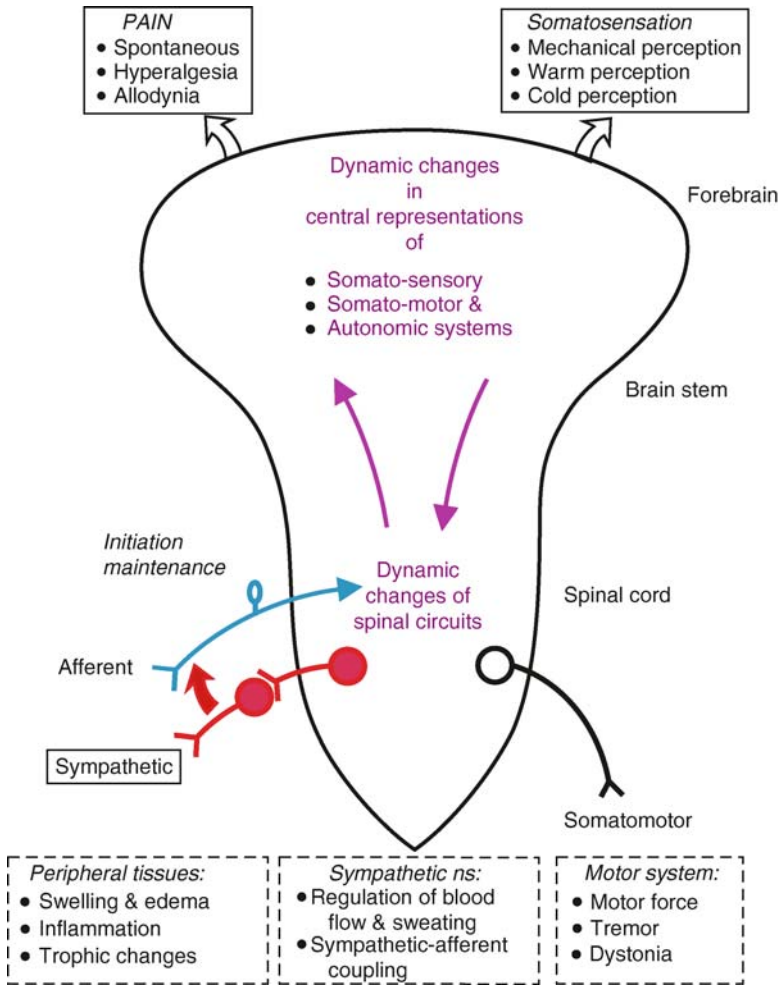
A General Explanatory Model

Results obtained in experiments on human CRPS patients and quantitative clinical data clearly set the stage for the formulation of hypotheses that can be tested experimentally using various *in vivo* or *in vitro* animal models (which include by definition human models). Research on mechanisms should focus on quantifiable symptoms which can be observed in the patients (e.g., mechanical allodynia, spontaneous pain, tremor, changes of blood flow, swelling, etc.). Each symptom may be generated by more than one mechanism, depending on the type of CRPS patient. Experimental models to study the underlying mechanisms of CRPS cannot represent CRPS I or II as such. For this purpose the human patient is the best model. A general explanatory model must fulfill the following main criteria (Fig. 7):

1. CRPS is a neurological disease of the CNS involving sympathetic, afferent (sensory) and ►motor systems [6]. It is hypothesized that the CNS orchestrates the sensory, motor, autonomic, inflammatory and trophic changes, which are then reflected in the typical clinical phenomenology.
2. Important characteristics of CRPS I are signs of inflammation with edema and vasodilation in skin (increased cutaneous temperature); therefore an inflammatory process in the periphery is discussed. C*utaneous vasodilatation* is particularly prominent at the beginning of CRPS I in the first 2–4 months, but later may reverse into vasoconstriction when CRPS I is becoming chronic [1,2]. By the same token, the inflammatory changes also appear to be particularly prominent in the early stages of CRPS.
3. Both central and peripheral mechanisms interact with each other. This interaction may occur by way of various channels. The CNS receives information from the periphery via the hard-wired afferent nociceptive and non-nociceptive neurons and possibly chemical signals (e.g., cytokines from inflamed tissues). The CNS sends its information to the periphery through sympathetic channels, possibly neuroendocrine systems (e.g., the sympatho-adrenal system) or perhaps even by antidromic activity in peptidergic primary afferent neurons. The central neural programs regulating sympathetic, somatomotor and afferent systems may be changed due to a mismatch between the sensory representations and the motor and autonomic representations in the forebrain (which is clinically reflected in the changes related to the motor, sensory and autonomic systems).



Complex Regional Pain Syndromes: Pathophysiological Mechanisms. Figure 6 a The micromilieu of nociceptors. The microenvironment of primary afferents is thought to affect the properties of the receptive endings of myelinated (A) and unmyelinated (C) afferent fibers. This has been particularly documented for inflammatory processes, but one may speculate that pathological changes in the direct surroundings of primary afferents may contribute to other pain states as well. The vascular bed consists of arterioles (directly innervated by sympathetic and afferent fibers), capillaries (not innervated and not influenced by nerve fibers) and venules (not directly innervated but influenced by nerve fibers). The micromilieu depends on several interacting components: Neural activity in postganglionic noradrenergic fibers (1) supplying blood vessels (3, BV) causes release of noradrenaline (NA) and possibly other substances and vasoconstriction. Excitation of primary afferents (Aδ- and C-fibers) (2) causes vasodilation in precapillary arterioles (mainly release of calcitonin gene-related peptide, CGRP) and plasma extravasation in postcapillary venules (C-fibers only) by the release of substance P (SP) and other vasoactive compounds (e.g., CGRP). Some of these effects may be mediated by non-neuronal cells such as mast cells (MC,4) and macrophages (MP, 5). Other factors that affect the control of the microcirculation are the myogenic properties of arterioles (3) and more global environmental influences such as a change of the temperature and the metabolic state of the tissue. Modified from [20]. (b) Hypothetical relation between sympathetic noradrenergic nerve fibers (1), peptidergic afferent nerve fibers (2), blood vessels (3) and macrophages (4). The activated and sensitized afferent nerve fibers activate macrophages (via substance P release). The immune cells start to release cytokines, such as tumor necrosis factor α (TNF-α) and interleukin 1 (IL1), which further activate afferent fibers by enhancing sodium influx into the cells. Substance P (and CGRP) released from the afferent nerve fibers reacts with neurokinin 1 (NK1) receptors (CGRP receptors) in the blood vessels (arteriolar vasodilation, venular plasma extravasation; neurogenic inflammation). The sympathetic nerve fibers interact with this system on three levels: (i) via adrenoceptors (mainly alpha) on the blood vessels (vasoconstriction); (ii) via adrenoceptors (mainly beta) on macrophages (further release of cytokines), and (iii) via adrenoceptors (mainly alpha) on afferents (further sensitization of these fibers). Modified from [6].



Complex Regional Pain Syndromes: Pathophysiological Mechanisms. Figure 7 Schematic diagram summarizing the sensory, autonomic and somatomotor changes in complex regional pain syndromes I (CRPS I) patients. The figure symbolizes the CNS (forebrain, brain stem and spinal cord). Changes occur in the central representations of the somatosensory, the motor and the sympathetic nervous system (which include the spinal circuits) and are reflected in the changes of the sensory painful and non-painful perceptions, of cutaneous blood flow and sweating, and of motor performances. They are triggered and possibly maintained by the nociceptive afferent input from the somatic and visceral body domains. It is unclear whether these central changes are reversible in chronic CRPS I patients. These central changes possible also affect the endogenous control system of nociceptive impulse transmission. Coupling between the sympathetic neurons and the afferent neurons in the periphery (see bold closed arrow) is one component of the pain in CRPS I patients with sympathetically-maintained pain (SMP). However, it seems to be unimportant in CRPS I patients without SMP. Modified from [6].

According to the central hypothesis, the acute vasodilation might be due to inhibition of activity in cutaneous vasoconstrictor neurons, and the vasoconstriction might depend on decentralization supersensitivity of cutaneous blood vessels to impulses in cutaneous vasoconstrictor neurons. According to the peripheral inflammatory hypothesis, vasodilation might potentially be linked to the peptidergic primary afferent neurons with C-fibers, and therefore to the neurogenic inflammatory component. Activation of (probably a subset of) peptidergic primary afferent neurons leads to precapillary vasodilation mediated by release of calcitonin gene-related peptide (CGRP) and substance P and postcapillary plasma extravasation by release of substance P [6]. Furthermore, there is enough evidence from investigations of patients with CRPS I to show that blockade of the sympathetic supply to the affected extremity may be followed by a decrease of the edema (Fig. 5). Thus, how do we bring together the centrally generated components related to the afferent

(sensory), motor and sympathetic systems and the peripheral components related to inflammation and sympathetic-afferent coupling? Do these mechanisms in CRPS I patients operate independently or are they functionally linked, and if so, how can this link be explained? How does the brain generate and modulate the peripheral inflammatory processes?

Research based on these thoughts will radically change our approach to this pain syndrome in diagnostic classification and therapy. This is already visible in some investigations published recently, and clearly demonstrates how successful approaches based on basic research concepts can be [1,2].

Future Research Directions

CRPS patients exhibit changes that occur in systems processing noxious, tactile, and thermal information; in sympathetic systems controlling blood vessels, sweat glands, and possibly other targets; and in the somatomotor system. This constellation of signs indicates that the central representations of these systems are changed. The way these central changes are triggered by the peripheral trauma, which is often minor compared to the dramatic expression of the clinical phenomena, remains an enigma. However, based on the work of McCabe and Moseley [see 1,2], it can be hypothesized that the sensory feedback from the body tissues is no longer precisely, temporarily and spatially welded to the central somatic and autonomic motor programs represented in spinal cord, brain stem, hypothalamus and cerebral hemispheres. This "sensory-motor mismatch" results in the somatic motor, autonomic motor and sensory abnormalities (including pain). Furthermore, how these central changes relate to the peripheral inflammatory/immune changes is entirely unclear. However, these questions can now be investigated using the human patient and animals as models.

Finally, we cannot explain why pain and the other changes associated with the sympathetic nervous system (including swelling), the motor system and the somatosensory system may disappear, not only in CRPS patients with SMP but also in those without, after sympathetic blockade. Based on the clinical changes that can be measured quantitatively, hypotheses about the underlying mechanisms have to be formulated. These hypotheses should be tested by using a multidisciplinary approach, which includes clinical experimentation, human models and various types of animal models (*in vivo*, *in vitro*). This type of integrative research is a necessity if we are to unravel the mechanisms that operate in CRPS, and if we are to find out the organizing pathophysiological principles that orchestrate the different changes. It is essential that basic research in animal models, human beings and clinical studies of CRPS should be closely aligned.

Conclusions

The subject *sympathetic nervous system and pain* is a developing field in the clinics as well as in research. Research on CRPS with the aim to improve diagnostic criteria, classification and therapy has increased considerably. In future, this research will be better anchored in basic research on the systems affected (sympathetic nervous system, somatic and visceral ►sensory systems, motor system, ►central nervous system, immune system, etc.). Furthermore, research on the mechanisms of CRPS will be better integrated with the clinic. The directions to be taken in basic and clinical research should have the following priorities:

1. Basic research focusing on the brain in order to find out in which way the brain orchestrates the changes seen in the somatosensory, sympathetic and somatomotor systems.
2. Basic research focusing on the peripheral inflammatory and other peripheral processes, and on how these peripheral changes are linked to the central changes.
3. Studies to validate existing models and to develop new models of CRPS or its components.
4. Studies on research mechanisms giving rise to CRPS in susceptible individuals.
5. Research on CRPS serves as a model for exploration of the pathophysiological mechanisms in related clinically important fields, such as neural regulation of rheumatoid diseases, fibromyalgia, irritable bowl syndrome, inflammatory bowel disease or of the immune system, etc., [5,10].

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Complex Sound

Definition

A sound with more than one frequency component.

►Acoustics

Complex Trait

Definition

Complex trait is a trait or characteristic that is inherited in a fashion that does not follow strict Mendelian inheritance, because it may involve interactions between two or more genes.

Computational Approach

Definition

Part of neuroscience that includes mathematical modeling and simulations to understand the functioning of the nervous system.

Computational Biology

►Bioinformatics

Computational Model

Definition

A computer model is a computer program that attempts to simulate an conceptual model of a particular system with the aim of gaining insight into how the system operates.

Computational Modeling of the Respiratory Network

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Synonyms

Respiratory network; respiratory central pattern generator; respiratory CPG

Definition

►Respiratory network is a neural circuitry in the mammalian ►brainstem that generates the ►respiratory rhythm and complex pattern of neuronal activity controlling movement of respiratory muscles that provide ►lung ventilation and perform the vitally important function of ►breathing. Computational modeling of the respiratory network is a powerful tool for theoretical investigations aimed at increasing our understanding of the complex neural mechanisms involved in generation and control of the respiratory rhythm and motor pattern.

Characteristics

Generation of the Respiratory Rhythm: Concepts, Mechanisms and Computational Models

Respiratory Network: Location, Types of Neurons, and the Respiratory Pattern

The motor pattern observed during normal breathing (►eupnea) consists of three phases: ►inspiration (I), ►postinspiration (pI or E1), and late ►expiration (E2), which can be recognized in the integrated activity of the ►phrenic nerve and ►cranial nerves. This pattern originates within a bilateral column of neurons, called the ►ventral respiratory column (VRC), located in the ►ventrolateral medulla, and is controlled by inputs from other medullary and pontine regions. The VRC includes

several compartments arranged in the rostro-caudal direction: ►Bötzinger Complex (BötC), ►pre-Bötzinger Complex (pre-BötC), and rostral (rVRG) and caudal (cVRG) subregions of the ►ventral respiratory group (VRG). Respiratory neurons in these compartments are classified based on their temporal firing pattern (e.g., decrementing, augmenting) and the phase of activity relative to the breathing cycle, such as: early-inspiratory (early-I or I-DEC), i.e., ►inspiratory neurons with a decrementing discharge pattern; ramp-inspiratory (ramp-I or I-AUG), i.e., inspiratory neurons with an augmenting firing pattern; ►post-inspiratory neurons (post-I or E-DEC), i.e., neurons with a decrementing pattern during expiration; augmenting or stage II expiratory (aug-E or E-AUG or E-2), i.e., ►expiratory neurons with an augmenting pattern; ►pre-inspiratory neurons (pre-I or I-E/I) whose activity starts before the onset of inspiration and continues during inspiration. The BötC, with predominately post-I and aug-E neurons, is considered a major source of expiratory activity. The adjacent, more caudal compartment, the pre-BötC, contains circuitry essential for generating inspiratory activity. The activity of bulbospinal inspiratory (ramp-I or E-AUG) neurons of the rVRG, projecting to the phrenic motoneurons, is driven by the pre-BötC and inhibited by the inhibitory expiratory neurons of BötC and cVRG. The pontine respiratory regions include the ►Kölliker-Fuse (K-F) nucleus and ►parabrachial (PB) complex in the ►dorsolateral pons and several areas in the ►ventrolateral pons. Neurons in these areas exhibit phasic or tonic activity with inspiratory, expiratory or phase-spanning modulation and are involved in control of the respiratory pattern. Mechanosensory feedback from lungs provides strong modulation of the respiratory rhythm and pattern by controlling the timing of phase transitions and durations of inspiration and expiration. Specifically, lung inflation activates ►pulmonary stretch receptors (PSRs) that project to the ►pump (P) cells in the ►nucleus tractus solitarii (NTS), which transmit information on lung inflation to the VRC and pontine nuclei. This feedback provides the ►Hering–Breuer reflex consisting of shortening (advanced termination) of inspiration and prolongation of expiration.

Network Mechanisms for Respiratory Rhythm and Pattern Generation and Network Models

Computational models of the respiratory network have been in development for several decades. Early computational models focused on the network interactions between different types of respiratory neurons and did not consider possible contributions of the intrinsic, biophysical properties of neurons. Generation of the respiratory rhythm in these models was based on a network concept suggesting that the respiratory rhythm results from sequential phase switchings, such as an inspiratory off-switch (IOS, transition from inspiration to expiration) and an expiratory off-switch (EOS, transition from expiration to inspiration). These phase switchings were proposed to result from the reciprocal (mostly inhibitory) interactions among different types of respiratory neuron populations. The early network models employed relatively simple activity-based models of single neurons in which the output neuronal (or population) activity was described by single continuous variables representing the neuronal firing rate. For example, Duffin [1] proposed a model of the respiratory network consisting of two inhibitory (I-DEC and E-BÖT) and one excitatory (I-AUG) neurons, that generated two-phase (inspiration–expiration) oscillations based upon mutual inhibition between the I-DEC and E-BÖT neurons. Both phase switching mechanisms (IOS and EOS) in this model were based on the adaptive properties of the I-DEC neuron and the reciprocal interactions between the two inhibitory neurons.

A series of three-phase network models were developed based on a conceptual schematic proposed by Richter et al. [2] that postulated that the respiratory cycle consists of three phases: inspiration, postinspiration, and late expiration. The IOS mechanism in these models involved late-I neurons that started firing by the end of inspiration, reached peak activity at the transition from inspiration to expiration, and provided the initial inhibition of inspiratory neurons. The early three-phase models usually used the activity-based models of units for simulating single neurons or neural populations. The model proposed by Botros and Bruce [3] included five neuron populations: I (inspiratory with a ramp-I pattern); early-I; late-I, post-I and E (expiratory). The interconnections among these populations were assigned in accordance with the Richter scheme [2]. The model generated a stable respiratory rhythm and reproduced realistic activity profiles of all five neuron populations incorporated. Some effects of pulmonary mechanosensory feedback on the respiratory pattern were also reproduced.

Balis et al. [4] developed the first model of the respiratory network based on interacting populations of respiratory neurons using simplified, "spiking", ►integrate-and-fire models of single neurons. Their network model contained six neuron populations: one excitatory (I-AUG type), four inhibitory (I-DEC, E-AUG, E-SYM, and E-DEC), and an additional I-E/I (pre-I) population. Some key connections in the model were assigned from a spike-train analysis of multiple recordings performed by the same group. Interestingly, depending on the model parameters the respiratory pattern could be generated with or without an involvement of the I-E/I population.

Rybak et al. [5] built a series of network models with more complicated, ►conductance-based models of single neurons and analyzed possible roles of intrinsic

neuronal properties in the genesis of the respiratory rhythm. Several distinct network schematics were comparatively investigated. One version of this model is shown in Fig. 1. The model includes six respiratory neurons: early-I, ramp-I, late-I, post-I, aug-E (or E2), and pre-I. The IOS mechanism operates via the late-I neuron as proposed by the Richter scheme [2]. The EOS mechanism involves the pre-I neuron, which is inhibited during expiration, but when released from inhibition provides an initial activation of early-I and ramp-I neurons; the early-I neuron then inhibits post-I and aug-E neurons, hence completing the switch to inspiration.

This model includes a simplified model of the lungs and PSRs that provide pulmonary feedback to the respiratory network (Fig. 1a). This feedback is excitatory to the late-I and post-I neurons and inhibitory to the early-I neuron, allowing the expression of the Hering–Breuer reflex. Disconnecting the vagal feedback ("►vagotomy") causes a prolongation of inspiration and an increase in the amplitude of integrated phrenic discharges (Fig. 1b).

The model generates a realistic respiratory pattern, reproduces membrane potential trajectories of individual respiratory neurons (Fig. 1b), and shows proper changes in the respiratory pattern and firing activities of individual respiratory neurons under different conditions, including vagotomy and application of various stimuli activating afferent nerves. At the same time, this model (as well as other network models, such as those described above) failed to reproduce some important behaviors obtained from in vitro studies of the neonatal rodent system, specifically the persistence of rhythmic activity after inhibition in the network was blocked (see below).

Pre-Bötzinger Complex and Rhythm Generation In Vitro

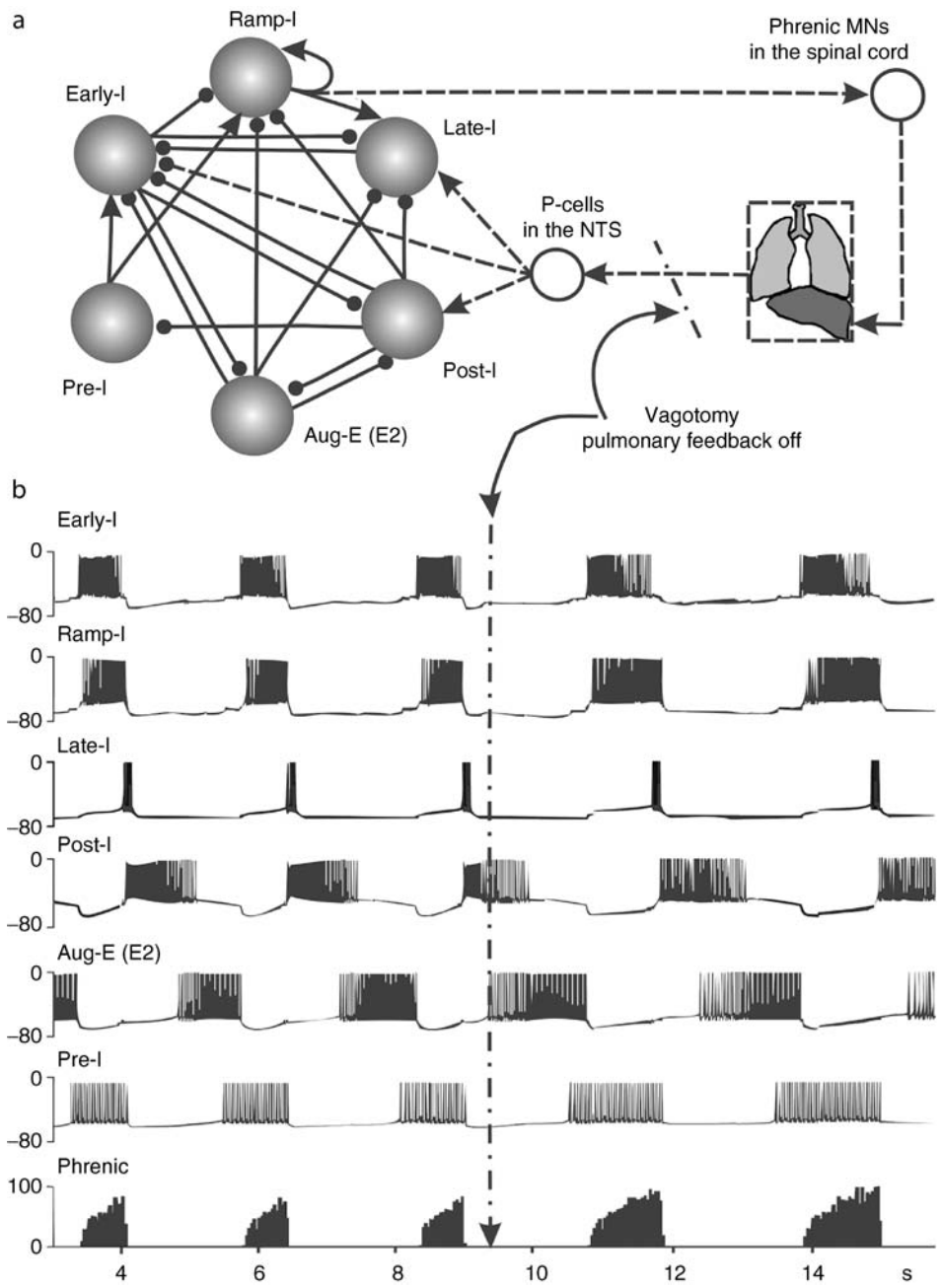
A fundamentally distinct concept of respiratory rhythm generation was derived from the neonatal in vitro studies. The important discovery has been that a subregion of the VRC, called the pre-Bötzinger Complex (pre-BötC), contains a population of excitatory interneurons that can intrinsically generate an inspiratory-like rhythm [6]. This rhythm was shown to persist after blockade of synaptic inhibition, indicating that the pre-BötC may contain special cells with intrinsic ►bursting properties. Butera et al. [2] developed and analyzed a series of computational models of ►bursting pacemaker neurons and populations of these neurons with mutual excitatory connections. In these models, the intrinsic bursting activity was based on a subthreshold activating, slowly inactivating ►persistent sodium current (I_{NaP}) as the essential burst-generating, inward cationic current. The rhythmic bursting cycle in these models was controlled by the slow kinetics of inactivation and recovery from inactivation of I_{NaP}. This kinetics was shown sufficient to generate voltage-dependent oscillations with the frequency spanning the range of bursting frequencies observed experimentally. Simulations performed have shown that the excitatory synaptic interactions coupled with I_{NaP} activation can readily synchronize cellular bursts and produce population bursting (Fig. 2a, b). Generation of this rhythm does not require inhibitory interactions; this can explain the persistence of the in vitro oscillations after inhibitory synaptic transmission was blocked. It was also shown that even a small fraction of intrinsically bursting cells (5–10%) can produce a synchronized bursting activity of the entire population. Moreover, synchronized population rhythms may occur even if none of the cells are in the intrinsic bursting state [7]. Elevation of tonic drive to the population reduces burst duration and increases burst frequency (see Fig. 2c) and, finally, switches population activity from bursting to a regime of sustained asynchronous activity (Fig. 2d).

This and a series of other related models were able to reproduce many characteristics of the pre-BötC activity in vitro, including multiple modes of activity (silence, bursting, and tonic) and a voltage-dependency of burst frequency.

Network-Based Versus Pacemaker-Driven Mechanisms for Respiratory Rhythmogenesis and a Hybrid Pacemaker-Network Model

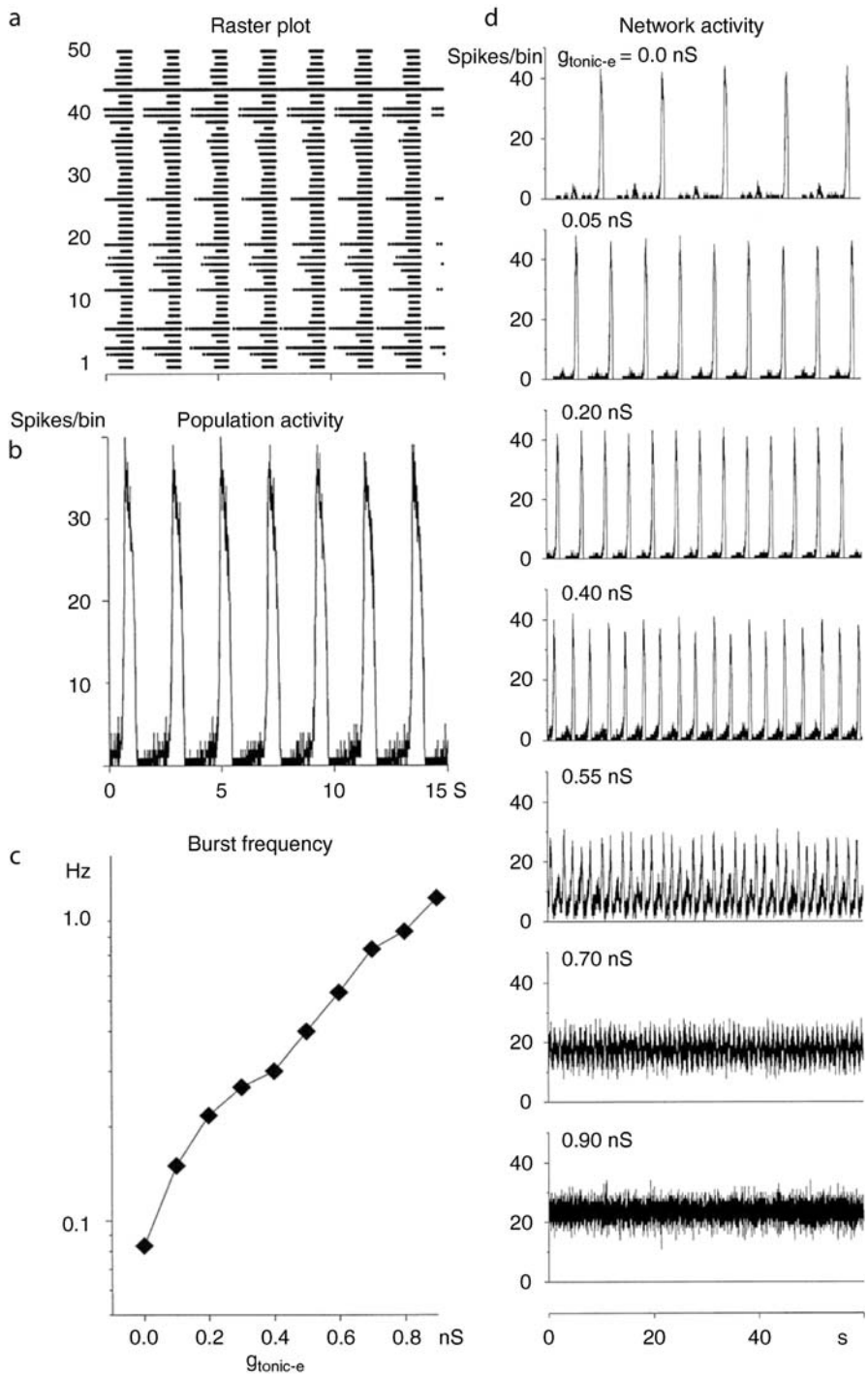
As described above, network models where able to reproduce many characteristics of the respiratory ►CPG including the generation of a realistic respiratory motor pattern and its alteration under different conditions. However, these models have failed to reproduce some characteristic behaviors observed in the reduced in vitro preparations and, specifically, the maintenance of the respiratory rhythm after blockade of synaptic inhibition. Alternatively, the pacemaker-based models, developed to fit to in vitro data, could not explain many behaviors observed in vivo, such as the Hering–Breuer and other respiratory reflexes, and independent regulation of the duration of each respiratory phase. For example, the pacemaker-based model could not reproduce ►apneusis, a breathing pattern characterized by a significantly prolonged inspiration (up to several seconds) alternating with short expiratory intervals. Moreover, the pattern of rhythmic inspiratory discharges obtained from the reduced in vitro preparations and reproduced by the pacemaker-based models was characterized by a decrementing shape of inspiratory discharges (see Fig. 2), which differed from the augmenting shape of phrenic discharges observed during eupneic breathing in vivo and rather resembled the decrementing bursts observed during ►gasping in vivo.

The contradiction between the network-based and pacemaker-based concepts and models can be resolved by postulating that: (i) the pre-BötC, while capable of bursting intrinsically when isolated, is embedded in the



Computational Modeling of the Respiratory Network. Figure 1 A network model of the respiratory CPG. (a) The schematic of a network model. Large spheres represent different respiratory neuron types. Excitatory and inhibitory synaptic connections are shown by arrows and small circles respectively. Each neuron also receives external excitatory drive (not shown). The pulmonary feedback loop that includes the lungs is shown by *dash lines*. (b) Model performance. All traces, except the bottom one, show membrane potential trajectory of particular respiratory neurons (indicated at *left*); the *bottom trace* shows the integrated phrenic activity. The *dash-dot line* indicates the moment of vagal feedback disconnection ("vagotomy"). Modified from [5] with permission.

larger brainstem respiratory network and its behavior as a part of the network becomes dependent on the interactions with other respiratory neural populations and (ii) the respiratory rhythmogenesis per se is state dependent, and therefore the rhythm may be generated by either a network-based or pacemaker-driven mechanisms, or their specific combinations depending on the conditions [8–10].

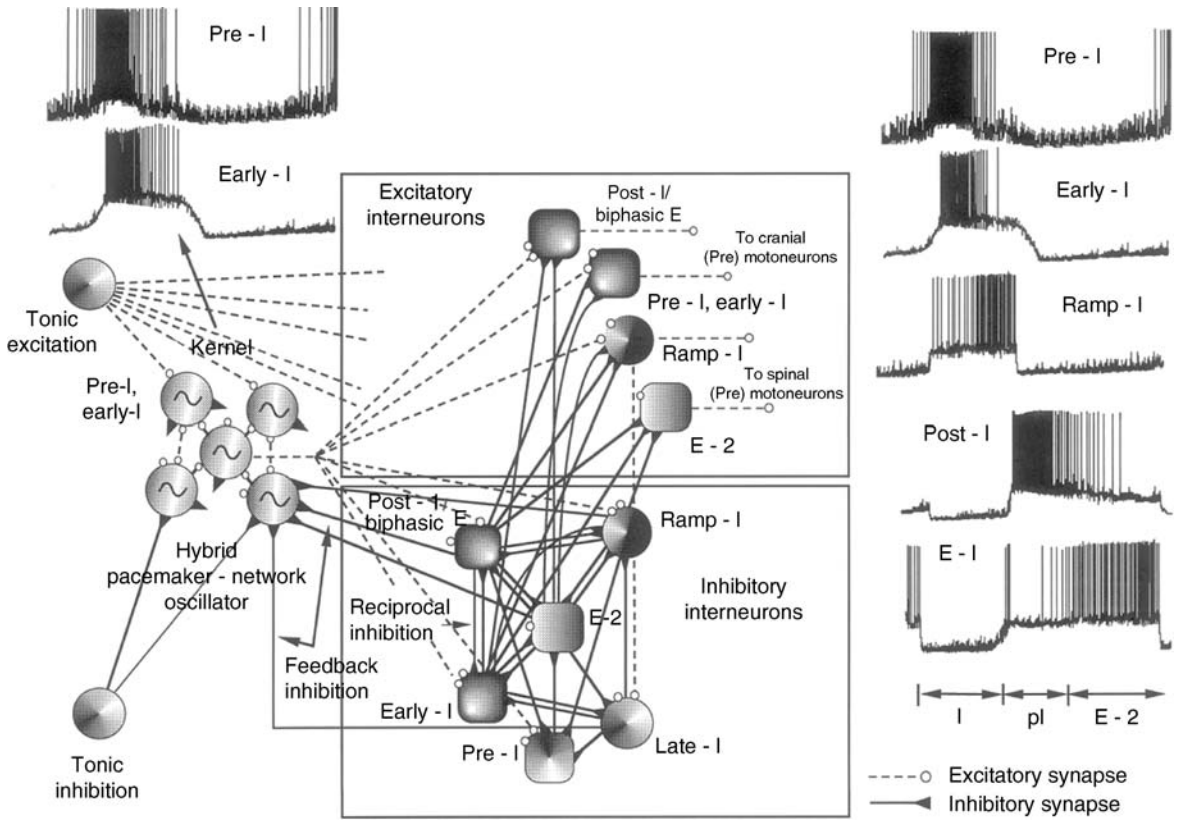


Computational Modeling of the Respiratory Network. Figure 2 Modeling the intrinsic bursting activity of the pre-Bötzinger Complex in vitro. Simulations are shown for a heterogeneous population of 50 voltage-dependent bursting neurons (see raster plot at *left* in a) coupled by fast excitatory synaptic connections. All neurons incorporate the persistent (slowly inactivating) sodium current (I_{NaP}). The population receives excitatory tonic drive. Heterogeneity and the cells' voltage-dependent properties result in temporal dispersion of spiking within the pre-BötC population. Population oscillations (b) generated by the model are similar to those recorded from the isolated pre-BötC in vitro. Population activity was obtained by calculating histograms (10 ms bins) of spike times across the 50 neurons. Control of pre-BötC population bursting frequency by tonic excitatory synaptic input ($g_{tonic\text{-}e}$) is shown in (c) and (d). Elevation of this input (from *top to bottom* in d) increases burst frequency and, finally, switches the population activity from bursting to sustained asynchronous activity. Modified from [7] with permission.

Based on these ideas, Smith at al. [10] proposed a hybrid pacemaker-network model in which the pre-BötC excitatory kernel, with I_{NaP}-dependent bursting pacemaker properties, was embedded into an inhibitory network. The schematic of this model is shown in Fig. 3. The network model contains several populations of inspiratory and expiratory neurons (pre-I, early-I, ramp- I, late-I, post-I/biphasic-E, and late-E (aug-E or E-2)) simulated using populations of conductance-based single neuron models. It was shown that this model can operate in multiple rhythm-generating regimes depending on the expression of voltage-dependent pacemaker properties in the kernel cells and on the inhibitory network interactions. In the pacemaker (kernel)-driven mode, the inspiratory bursting activity in the pre-BötC results from the interactions between the pacemaker properties and tonic and phasic excitatory and inhibitory inputs. With the system operating in this mode, oscillation frequency is controlled by tonic excitation/inhibition as in the isolated pre-BötC in vitro. In the network-driven mode, the kernel pacemaker neurons operate in the regime of sustained activity. In this state, the network feedback inhibition is required for ▶inspiratory phase termination. The inhibitory hyperpolarization resets I_{NaP} in the pre-BötC cells, allowing recovery from current inactivation, and the next inspiration is initiated when the inhibition declines. Analysis of the model has demonstrated that this hybrid model can be transformed dynamically between the above modes with specific changes in model parameters.

State-Dependent Generation of the Respiratory Rhythm: The Ponto-Medullary Model

As described above, the functional state of the pre-BötC neurons with I_{NaP}-dependent bursting properties can be controlled by excitatory tonic drive and phasic synaptic inhibition (see also in [7]). Specifically, a relatively high excitatory drive can depolarize these neurons producing



Computational Modeling of the Respiratory Network. Figure 3 The hybrid pacemaker-network model. The respiratory network consists of interacting populations of different excitatory and inhibitory interneurons and incorporates the excitatory pacemaker-driven "kernel", representing the pre-BötC that includes the populations of neurons (pre-I and early-I types) with I_{NaP} current (their activity is shown at the *top left*). Follower excitatory interneurons (see examples of activity patterns at the *top right*) generate synaptic drive via parallel transmission pathways to cranial and spinal (pre)motoneurons. Interconnected inhibitory interneurons generate temporal patterns of synaptic inhibition that project to the pre-BötC via feedback connections and the to the follower excitatory populations to sculpt pre-motor output activity. Modified from [10] with permission.

inactivation of I_{NaP} and putting these neurons to the state of tonic spiking. In addition, phasic inhibition can entrain a rhythmic rebound bursting resulting from the periodical disinhibition of pacemaker neurons. Hence tonic drive from supramedullary centers (e.g., from the ►pons) may control the functional state of the pre-BötC directly, via excitatory drive to the pre-BötC, as well as indirectly through the activation of post-I neurons providing phasic inhibition to the pre-BötC. As a result, pontine inputs to both the pre-BötC and BötC may change the operating rhythmogenesis mechanism via alteration of the functional state of pre-BötC neurons.

Rybak et al. [9] developed a model of the ponto-medullary respiratory network that employed the above state switching mechanism. Fig. 4 shows the schematic of this model and its performance under different conditions. The model consists of interacting populations of neurons modeled using conductance-based single neuron models. An attempt has been made to integrate known cellular-, network-, and system-level mechanisms contributing to respiratory rhythm generation and control, and accumulate all advantages of the previous models. Also in contrast to the previous models, this model has considered a spatial organization of "respiratory" compartments in the ►medulla (VRC) and pons by incorporating spatially separate compartments, such as rVRG, pre-BötC, BötC (all in VRC) as well as rostral (rPons) and caudal (cPons) parts of the pons. Each compartment includes neural populations known to be dominantly present in this region. Synaptic connections between neural populations within the VRC (i.e., between the ramp-I, early-I, late-I, post-I, aug-E and pre-I populations) define the basic circuitry for IOS and EOS mechanisms, which were similar to those operating in the network model shown in Fig. 1. At the same time, the pre-I population of the pre-BötC contains neurons with I_{NaP}-dependent pacemaker properties. Reciprocal excitatory connections between the medullary ramp-I and the pontine I-mod and IE-mod populations, and between the medullary post-I and the pontine IE-mod and E-mod populations, provide I-, IE- or E-modulation of the activity of the corresponding pontine populations. The model suggests that reticular neurons from the caudal pons (the tonic population) provide excitatory tonic drive to the majority of medullary respiratory neurons. Similar to the network model shown in Fig. 1, pulmonary mechanosensory feedback controls the activity of the key neural populations involved in IOS and EOS mechanisms (via activation of the late-I, post-I and ramp-I populations and inhibition of the early-I population) and hence contributes to regulation of the durations of respiratory phases through the Hering–Breuer reflex. In addition, this feedback suppresses the activity of the pontine neural populations that receive excitation from the medullary populations (I-mod, IE-mod, E-mod). Importantly, the IOS and EOS mechanisms in this model operate under control of both pontine input and pulmonary feedback, which both are excitatory to the late-I, ramp-I and post-I populations.

The performance of the model under different conditions is shown in Fig. 4b–e. With pons intact, the model generates a stable "eupneic" respiratory rhythm and exhibits realistic firing patterns and membrane potential trajectories of respiratory neurons (see Fig. 4b). Specifically, the bursts of ramp-I neurons as well as phrenic discharges exhibit augmenting patterns. The pulmonary feedback to the medulla provides the Hering–Breuer reflex, so that disconnecting this feedback ("vagotomy") produces an increase in the amplitude and duration of phrenic discharges (Fig. 4c) reflecting the loss of the Hering–Breuer reflex.

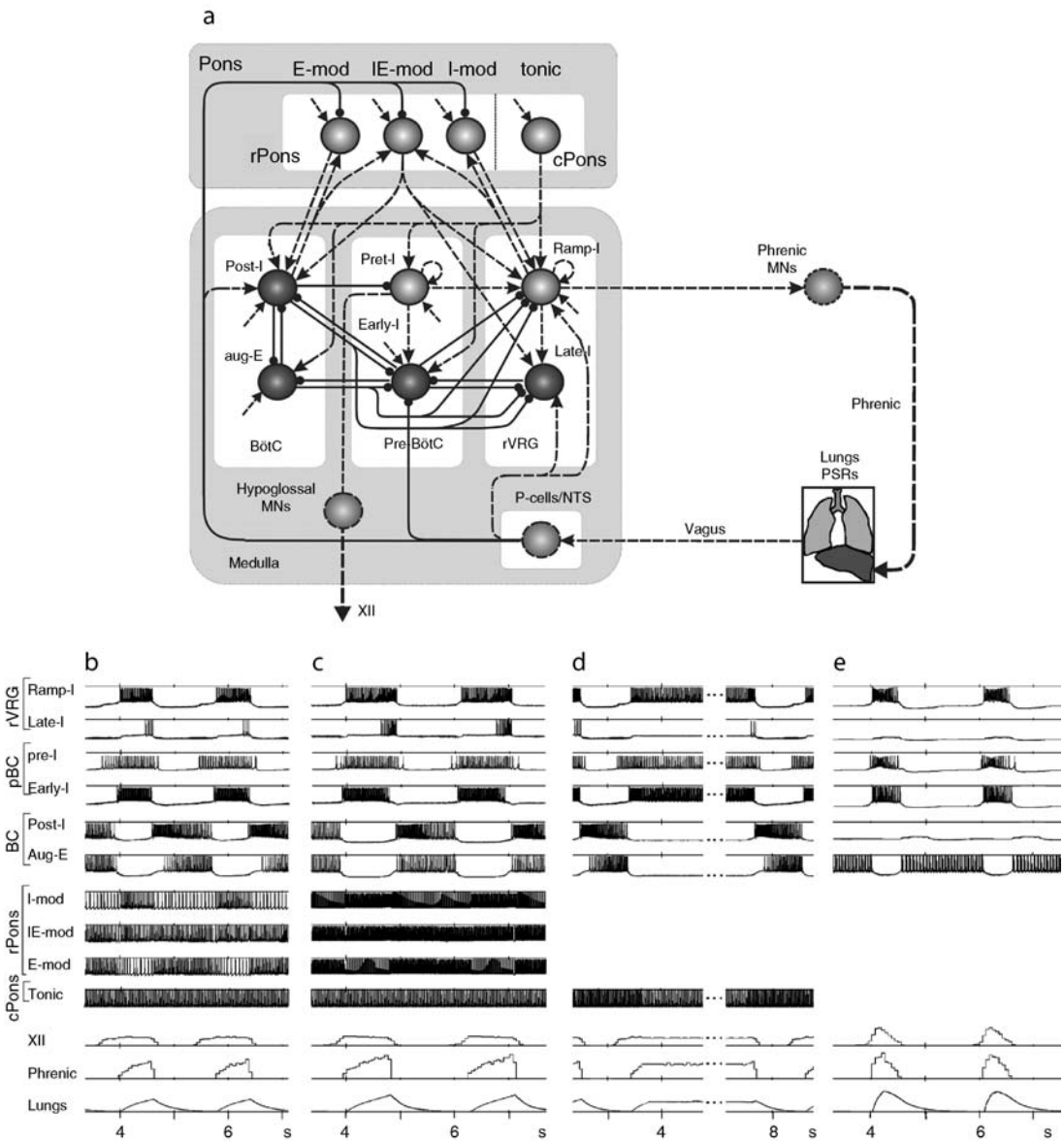
Disconnection of vagal feedback also eliminates the suppressing influence of vagal afferents upon the pontine I-mod, IE-mod and E-mod populations (Fig. 4a) and hence increases the role of these pontine populations in the control of respiratory phase switching. This control is provided via the same medullary IOS and EOS circuits that are controlled by pulmonary vagal feedback when the latter is intact.

As shown previously in cats and rats, a removal of the rostral pons or chemical blockade of respiration-related structures within this region produces apneusis, and a complete removal of the pons and rostral medullary structures in vivo can produce gasping-like phrenic bursts with decrementing phrenic discharges. Similarly, a removal of rPons in this model converts the normal breathing pattern to apneusis (Fig. 4d), and a complete removal of the pons (additional removal of cPons) produces gasping-like (or in vitro-like) oscillations characterized by a decrementing phrenic discharges (Fig. 4e). More recent versions also consider the regulatory role of inputs from rostral medullary neurons such as ►retrotrapezoid nucleus neurons, which have been proposed to convey tonic input related to chemosensory function.

This model (as well as the hybrid model described above) suggests that the operating rhythm-generating mechanism (network-based, pacemaker-driven or hybrid), particular that is engaged and expressed under conditions, depends on the functional states of the pre-BötC and other VRC compartments (e.g., BötC), which in turn are controlled by multiple network interactions within the medulla as well as by various supramedullary (e.g., pontine) and afferent (mechano- and chemosensory) inputs carrying information on the functional state and metabolic needs of the system.

Synopsis

Although many cellular and network properties involved in respiratory rhythm and pattern generation remain unknown, there is an emerging understanding



Computational Modeling of the Respiratory Network. Figure 4 The ponto-medullary model of the respiratory CPG. (a) Model schematic. Each sphere represents a population of 50 neurons. *Dark and light large spheres* are excitatory and inhibitory populations respectively. *Dashed lines with arrows* represent excitatory synaptic connections and *solid lines* ended with small circles show inhibitory connections. *Additional arrows* at the population circles indicate external excitatory tonic drive to each population. (b–e) Model performance under different conditions. The *top traces* (except the bottom three) show membrane potential trajectory of one, randomly selected neuron from each population; the three *bottom traces* show integrated hypoglossal (XII) and phrenic activities and lung volume (the *bottom trace*). (b) The performance of the intact network ("eupnea"). (c) "Vagotomy" – the vagal feedback in the model is disconnected. (d) "Apneusis" produced by removal of rPons. (e) Complete removal of the pons switches the system to the state in which the rhythm in the network is completely driven by bursting pacemaker activity originating in the pre-BötC. Modified from [9] with permission.

that the operating neural mechanisms involved are state-dependent and entail complex cross-level interactions between multiple cellular-, network-, and system-level processes. Computational modeling at all levels of complexity is expected to play an increasing role in analyzing the complex mechanisms underlying respiratory network function and the neural control of breathing.

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Computational Motor Control: ERN

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The nervous system analyses sensory information (►Sensory systems) and orchestrates motor commands (►Motor control). Many artificially engineered systems face similar challenges. Following the notion of cybernetics, we strive to boost both scientific and technological research by exploring the differences between artificial control theory (►Adaptive control; ►Computer-neural hybrids; ►Control theory; ►Nonlinear control systems; ►Signals and systems) and the biological motor control.

Computational motor control covers all applications of quantitative engineering tools as well as other mathematical tools for the study of the biological movement control system, which includes the joints, muscles, sensory organs and of course the nervous system.

For example, ►feedback control, ►adaptive control, and ►bayesian statistics, represent such computational tools that were employed in the study of the biological motor control system, see also [1–4].

The applications of computational motor control are bidirectional: on the one hand control theory knowledge is employed to generate new theories for the biological motor control and on the other hand we draw inspiration from the biological motor control in order to develop new control strategies for artificial devices.

In the following two sections we describe this interplay between science and technology and introduce the main concepts in the field of computational motor control that are further defined in the relevant keywords throughout the encyclopedia.

Control Theory and Our Understanding of the Biological Motor Control System

Brain researchers have always used technical analogies stimulated by the status of the technology at the time of writing. For a recent review of insights from engineering theory that can shed some light on biological complexity see [5]. These analogies are very useful pedagogically and they could also be useful scientifically as long as they are accurately stated. The best way to accurately state an analogy is by means of a mathematical computational model. In the 50s the servo-mechanism was popular, and at that time Ragnar Granit [6] wrote that the concept of servo-control is practically as old as experimental physiology and could be traced back to Claude Bernard's idea about the *constancy of the internal environment* (1865). However, once the model is treated with a specific mathematical model, one can study the gain of the feedback and stability behavior, which are part of the feedback servo-mechanism control theory and were not existent at the time of Claude Bernard. The introduction of quantitative comparison of physiological data to the computational model paved the way to new discoveries, such as the time-varying gain [7] and the typically low gain and large delays [8] that generated new understandings and pushed researchers towards the notion of adaptive control.

Feedback Control (►Control) is the first technique taught in any control engineering class [9]. Computational motor control evolved as part of the field of biological cybernetics and the origin of the word cybernetics refers to feedback control and indeed in the early models for motor control, feedback control was the main analogy and modeling tool [7,10].

In parallel to the development of ►adaptive control theory, physiologists have noticed that the simple servo theory does not properly describe the biological motor control system since the gains are low and changeable,

and the delay does not enable proper control of rapid movements [8]. The delay problem is partially resolved by equilibrium theories (see ►Equilibrium point control) where the feedback is performed instantaneously by the muscle's impedance (►Impedance control).

Another prominent feature of the biological motor control system which is not addressed by the servo theory as well as by most modern engineering theories is the redundancy of the biological motor system [11] which enables obtaining the same goal by activating many possible muscle unit combinations (see ►Coordination).

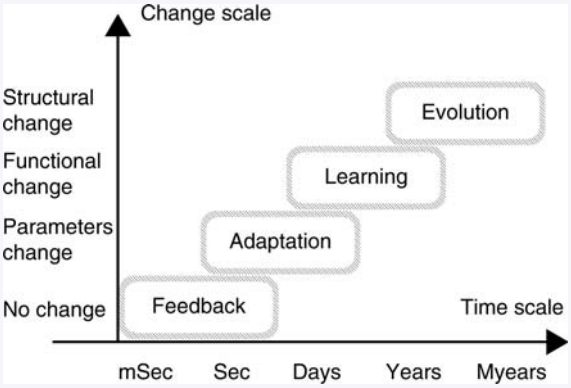
Most notably, adaptive control theory was required in order to address the limitations of the servo theory and is being increasingly employed in many studies of the biological motor control system [12–16].

The Hierarchy of Feedback Adaptation Learning and Evolution

Adaptation in the wide sense (WSA) is accommodation to the environment, in other words, any processing of sensory information that eventually changes the motor behavior in one way or the other. Figure 1 presents a map of four instances of this phenomenon where the coordinates of this map are time-scale and majority of change. We start with a description of the system approach and then move to address each type of the WSA separately to clarify the scope of each part in this structural temporal hierarchy.

Structural Temporal Hierarchy

A prominent tool of the engineering approach is the block diagram and we use it here to describe the various notions in the proposed structural temporal hierarchy.



Computational Motor Control: ERN. Figure 1 The temporal structural hierarchy of wide sense adaptation in the motor control system. Feedback, Adaptation, Learning and Evolution are instances of wide sense adaptation where sensory information is integrated and employed to change the control signal in various techniques and time scales.

Figure 2 demonstrates such a diagram in which each block is an input-output system. The output is a function of the input. The term function is used here in the wide sense to include transfer function that implies the existence of dynamics and internal state variables within the system as well as stochastic function that implies the presence of noise or uncertainty.

When we think about a control problem we usually have at least two systems: The controller and the controlled system. For example if we wish to control the position of the hand, we have the controlled system on the one side, i.e., the relation between the neural command to the muscles and the position of the hand, and the controller on the other, i.e., the relation between the intended movement and the neural signals to the muscles implemented by the brain. (Other distinctions are possible, such as considering the muscles as part of the controller as discussed further in the next subsection).

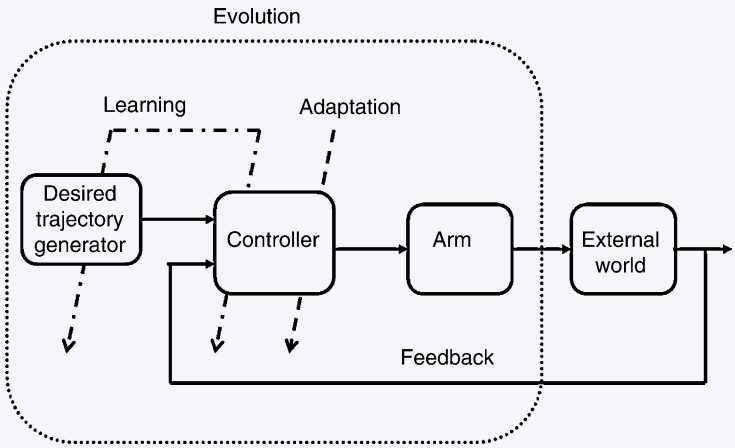
A prominent feature of the biological system is to use the sensory information about the actual position of the hand in order to improve the control of its position. This simple idea was used by engineers from the beginning of cybernetics (in part following observations of nature) and was later developed to include adaptive control. We follow the engineering terminology and use it to define a hierarchy of methods to improve the control signal and then try to use it to describe the brain as it controls movements. The basic idea of this hierarchy was first presented in [4] and here we further extend and more accurately define and demonstrate it. The terms feedback, adaptation, learning and evolution that are used here to describe this hierarchy are overloaded with various meanings and interpretations, therefore it is crucial that we properly define what we mean by each part of the hierarchy. We start from choosing the appropriate definition from the dictionary and then further define and demonstrate what we mean in the context of the hierarchy and the engineering and biological control systems.

Feedback

According to the Miriam-Webster Dictionary: "the return to the input of a part of the output of a machine, system, or process (as for producing changes in an electronic circuit that improve performance or in an automatic control device that provide self-corrective action)."

According to the Oxford Dictionary: "a. Electr. The return of a fraction of the output signal from one stage of a circuit, amplifier, etc., to the input of the same or a preceding stage."

We refer to a system as feedback control when sensory information is fed back to generate the control signal during the performance of the task (see Fig. 2). The signal flows from the sensory system to the control



Computational Motor Control: ERN. Figure 2 The hierarchy of wide sense adaptation in the control of arm movement. The biological motor control system is separated into three parts: the arm, which consists of the musculoskeletal system, the controller that may include internal models, state estimators as well as feedback controller, and the desired trajectory generator that represents higher brain functions. Feedback control changes only the control signals but does not change the functions of any part in the system. Adaptation may change the parameters of the controller, in particular parameters of the internal models. Learning may change the structure of the internal model and may also change the desired trajectory. Evolution can change each and every aspect of this system including the structure of the limb such as the number of joints in the arm. The external world influences the sensory feedback, which plays a crucial role in all these processes. Many studies manipulate the feedback by including force perturbations and altered visual feedback in order to excite these processes and analyze their properties. This diagram concentrates on the control of one arm movement, and therefore in this subsystem the external world is not influenced by the wide sense adaptation. However, in real life, outside the control experiments and rule-based games, the human brain has evolved to be capable of changing the environment and this capability is part of the learning process, therefore the learning process includes also changes in the strategy beyond changing the internal model and the desired trajectory, such as modifying the force perturbations by manipulating the environment.

system, this path could be long or short depending on the specific system; however, there is no change in the control system and the changes in the control signals are the result of changes in the sensory signals.

In the biological system the shortest path is typically described as the feedback reflex loop, which includes a monosynaptic pathway. However, there is a shorter pathway for feedback within the muscle. The simple mechanical property of stiffness (i.e. the force being proportional to the length of the muscle) could be referred to as feedback control, since the control signal (the force) is influenced by the outcome that is sensed by the length of the muscle. This last example demonstrates a limitation of the engineering approach, since the blocks usually hide the detailed structure, therefore if we define the control signal as neural input we would never note the internal feedback loops within the muscle and joint. In such block diagrams there is always a tradeoff between simplicity and accuracy and one should note that the hierarchy described here for a specific level of abstraction could be multiplied within each block.

Let us summarize this discussion with a formal definition of feedback control: Feedback Control: of a given input-output system is the usage of the output signal in order to generate the control signal in real time, i.e., the time scale of changes in the control signals is determined by the propagation of signals through the channels and the control system.

Figure 1 captures the main properties of feedback: signal flow in real time without changes in the system.

Adaptation

According to Miriam-Webster: "adjustment to environmental conditions: as (i) adjustment of a sense organ to the intensity or quality of stimulation (ii) modification of an organism or its parts that makes it more fit for existence under the conditions of its environment."

According to the Oxford Dictionary: "2. a. The process of modifying a thing so as to suit new conditions: as, the modification of a piece of music to suit a different instrument or different purpose; the alteration of a dramatic composition to suit a different audience."

Adaptive control is a control strategy where the controller can change its function to accommodate changes in the controlled system or in the environment. Here not only the signals are changed but also the control system is changed based on the sensory information

received. These changes in the system are typically slow compared to the time-scale of the feedback. The controller includes a finite set of adjustable parameters and a third system observes the flow of signals to and from the control system and determines how this set of parameters should change in order to improve some measure of performance.

Adaptive control: Changes in the parameters of the control system that are generated after observation of previous control and sensory signals in order to improve the future performance of the system over a well-defined task or measurements of performance.

Learning

According to Miriam-Webster: "**1 a** (1)**:** to gain knowledge or understanding of or skill in by study, instruction, or experience <*learn* a trade> […] **b:** to come to be able <*learn* to dance>."

According to the Oxford Dictionary: "1. The action of the vb. LEARN. a. The action of receiving instruction or acquiring knowledge; spec. in Psychol., a process which leads to the modification of behaviour or the acquisition of new abilities or responses, and which is additional to natural development by growth or maturation; (freq. opp. insight)."

While adaptation is a change in parameters of the controller that improves the performance in certain types of behavior, learning may generate a completely new behavior, as in skill acquisition, or may employ a new strategy to achieve the same task. In both cases the controller may change its structure. Such change in the biological system may include the recruitment of new brain areas or generation of a new neural circuit for a specific task. In artificial systems the controller may be replaced with another controller. At this point our technology does not provide an effective learning machine and it is highly possible that observing the biological system and modeling the neural control of movement may generate new control strategies that would later be used for artificial intelligent control, perfected by control engineers, and then return to serve as models for the brain.

Learning Control: change of the control system in order to generate a new type of behavior.

Evolution

According to Miriam-Webster: "**2 c** (1)**:** a process of continuous change from a lower, simpler, or worse to a higher, more complex, or better state; **4 b:** a theory that the various types of animals and plants have their origin in other preexisting types and that the distinguishable differences are due to modifications in successive generations."

According to the Oxford Dictionary: "6. Biol. a. Of animal and vegetable organisms or their parts: The process of developing from a rudimentary to a mature or complete state. c. The origination of species of animals and plants, as conceived by those who attribute it to a process of development from earlier forms, and not to a process of 'special creation.' Often in phrases doctrine, theory of evolution 7. The development or growth, according to its inherent tendencies, of anything that may be compared to a living organism (e.g. of a political constitution, science, language, etc.)."

In the proposed hierarchy, evolution is the last resort as it may take many years and it can potentially generate the largest change due to the evolution of a new species or in the engineering term, a new kind of controller.

Evolution: an arbitrary change in the controller that could include any change in structure, function, connectivity, parameter values, learning algorithms and adaptation protocols. The best change is chosen by survival of the fittest and therefore this process may be extremely long.

An Engineering Example

Consider a controlled system: $\boldsymbol{y} = \boldsymbol{P}(\boldsymbol{x}, \boldsymbol{u})$; $\dot{\boldsymbol{x}} = \boldsymbol{g}(\boldsymbol{x}, \boldsymbol{u})$, where $\boldsymbol{y}$ is the output, $\boldsymbol{u}$ is the input and $\boldsymbol{x}$ is the state, and a proportional controller $\boldsymbol{u} = \boldsymbol{k}(\boldsymbol{y}_d - \boldsymbol{y})$, where $\mathbf{y}_\mathrm{d}$ is the desired reference trajectory.

As long as $\boldsymbol{k}$ is constant, this is a simple feedback control. The sensed output $\boldsymbol{y}$ is used through the controller to change the control signal in real time, in this case immediately. Even if we introduced delay or dynamics to the controller, as long as the parameters of the controller are fixed this would still be called a feedback control system.

Now suppose that this feedback control that worked fine in the first design does not provide good performances due to changes in the control system or in the environment. We wish to choose $\boldsymbol{k}$ automatically to generate the best performance under this given structure. We may design an algorithm that observes the outputs and possibly also the inputs to the system and modify k accordingly. This scheme is called adaptive control and a typical requirement to avoid unstable behavior is that the time scale for the changes in the parameter is long compared to the time scale of the feedback loop. This is required in order to properly identify the system and adapt the parameters of the controller accordingly.

With this adaptive control we can face certain type of changes in the plant or the environment, however, a new task or severe changes in the plant or the environment (that would also be called new task) may require changes in the structure of the controller, e.g., one may consider adding integration or a lead or other elements from some given repertoire. In this example lets consider the repertoire of linear controller, i.e., finite number of poles and finite number of zeros in the transfer function of the controller.

An algorithm that would observe the inputs and outputs and would choose the optimal structure of the controller, i.e., the number of poles and number of zeroes, would be called a learning algorithm. Again this process should be slower than the typical time scale of adaptation in order to obtain enough information from the operation of the current controller to make a good decision.

Finally this whole framework of linear control might be wrong and a new generation could evolve based on gain scheduling or some neural network based controller (►Neural Networks for control).

Then again, after such an evolutionary process, e.g., in the case of neural network, the changes in the weights would be called adaptive control, changes in the connectivity, size and structure of the net would be called learning, an finally changes in the time of activation function or the underlying structure would be called evolution.

A Neurophysiological Example

Consider a reaching movement from an initial position to a given target (►Arm trajectory formation).

The ►equilibrium-point control [17–19] suggests that the brain specifies the end point, namely the resting length of the muscles, and then the arm moves to its equilibrium according to the law of physics. As long as the hand is not at the target there is an error signal that pushes the hand towards the target. This would be a classical feedback control. Other versions of the equilibrium control [18,19] are also based on feedback control and account for equilibrium trajectory.

Suppose that the subject holds a robotic manipulandum that exerts a velocity-dependent force perpendicular to the direction of movement [20]. In the first movement the subject generates a curved line and it seems that the feedback control is insufficient to generate a straight line. Then after practice the movement becomes straight and if the force field is stopped a curved movement in the other direction is generated, a phenomenon that was called after-effect. The after-effect is a clear sign that feedback was not the reason for the improved behavior and some change in the controller took place during this training period. We call such a change in parameters adaptation. The adaptive controller could be based on ►internal models [16] or on parametric changes in the Equiliberium-point (EP) signals or other control signals [21].

Now suppose that we introduce a completely new type of force field, which subjects are unable to adapt to within tens of trials, i.e. a force field, which is not within the natural repertoire of the adaptive control system. Two examples for such a force field are time-dependent forces and force fields that switch according to some sequence [22]. The natural adaptive control scheme is insufficient in order to compensate for such force fields, however, some individuals after prolonged practice in a proper training plan with proper cues and motivation may be able to learn this task, probably by employing new neural circuits or generating a major structural change of the control strategy. This would be a learning process.

Finally the force field might be stronger than the physiological limitations of the muscles, much stronger than the one that could be learned by increasing the muscles mass through training. In such cases, only evolution of a new species might solve this task if this task was essential for the survival of the subject for a large number of generations.

The adaptive nature of the biological system addressed in this essay is indeed the core of computational motor control, however, one should note that many other computational models and control methods are being employed in the study of the biological motor control including optimal control (see ►arm trajectory formation), optimal feedback control, stochastic control, ►information theory, ►nonlinear control systems, etc.

As new engineering and computational techniques are being developed by engineers and mathematicians they are quickly employed to describe the nervous system, and on the other hand as new behavioral and physiological phenomena are being observed they quickly inspire engineers to incorporate them into artificial systems – this is the essence of cybernetics and computational motor control and therefore the specific definition and list of related topics are ever growing.

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Computerized Stabilometry

►Stabilometry

Computer-Neural Hybrids

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Synonyms

Dynamic clamp; Neurally controlled animats; Hybrots; Embodied neural systems; Brain-machine interfaces; Brain-computer interfaces; Neuroprostheses

Definition

Device or experimental apparatus in which living neurons exchange information in a bi-directional way with an artificial system – a computer simulation or a physical device.

Exchange may involve intra-cellular signals and occur within a single neuron, or between pairs of neurons. Alternatively, the neural component may be made of multiple neurons, an entire neural population or even a whole organism, with its own intact sensory and motor systems. In this latter case, signals are exchanged extra-cellularly, with multiple stimulation and recording sites.

The artificial part may consist of simulated neurons, thus resulting in a hybrid neural circuit. It may include artificial sensor or actuator systems, as in ►neuroprostheses and ►brain-computer interfaces, or even consist of a whole physical or simulated body.

Description of the Theory

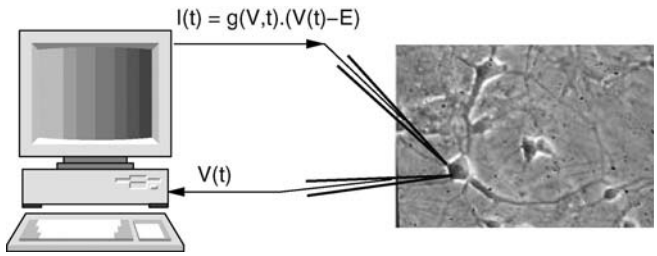
Description of the Structure

In computer-neural hybrids at single neuron level, an ►intra-cellular recording of the ►membrane potential of a neuron is used to calculate a current, which is then injected into the same or another neuron. In this way, it is possible to simulate artificial voltage-gated (Fig. 1) and/or ►synaptic conductances (Fig. 2). Both voltage measurement and current injection are made with glass micropipette electrodes. This technique is known as dynamic clamp [1].

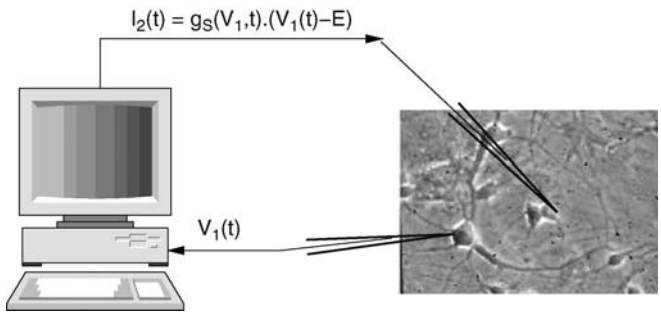
The artificial part of the dynamic clamp may consist of one or more simulated neurons. This would result in a hybrid neural circuit, made of both biological and artificial neurons. Dynamic clamp can be, and has been, implemented in various ways, ranging from analog circuits, to dedicated computer systems (e.g., digital signal processing boards), to software applications that exploit the computational power of modern computers.

In computer-neural hybrids that involve multiple neurons, both recording and stimulation usually occur extra-cellularly, through multiple electrodes or ►microelectrode arrays. Like in dynamic clamp, the multi-site neural signals are processed in real-time, but here the signal recorded from each electrode reflects the activity (population spikes and/or field potentials) of a small population of neurons. For this reason, the processing of the recorded neural signals often includes ►spike sorting modules, which result in multiple spike trains – one for each identified neuron in the population. Microelectrode arrays are also used to deliver electrical stimuli that excite the neural system by initiating action potentials in the neurons nearby (see Fig. 3).

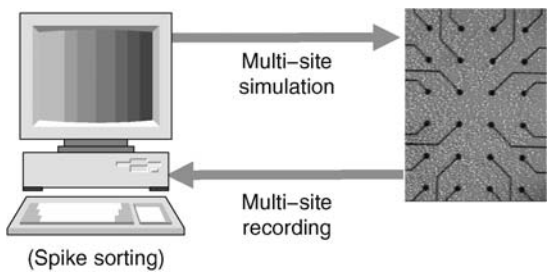
As both recording and stimulation occur extracellularly, in these hybrids the computer-neural interaction is less direct than in dynamic clamp. Nevertheless, the collective activity of the neural population can be



Computer-Neural Hybrids. Figure 1 Dynamic clamp simulation of a membrane conductance. The membrane potential V(t) is sampled and the computer calculates the membrane current, I(t), based on the model conductance g = g(V,t) and on its corresponding reversal potential, E.



Computer-Neural Hybrids. Figure 2 Dynamic clamp simulation of a synaptic conductance. The membrane potential of the pre-synaptic neuron, $V_1(t)$, is sampled, and the computer calculates the post-synaptic membrane current $I_2(t)$ based on the model synaptic conductance, $g_S = g(V_1,t)$ and on its corresponding reversal potential, E.



Computer-Neural Hybrids. Figure 3 Computer-neural hybrid a population level. The multi-site electrical activity of a neural population is recorded extra-cellularly through an array of micro-electrodes. Spike trains are then extracted from the signal and transformed into a patter of stimuli, which is applied to the same populations through selected micro-electrodes.

made to control the stimulation of the same population. Feedback may be used to maintain a specific dynamic regime, or to trigger adaptation phenomena.

Higher Level Structures: Neural Interfaces and Embodied Neural Systems

A particular class of computer-neural hybrids at population level is that of brain-machine interfaces (BMIs) or neural interfaces [2,3], in which an artificial device communicates directly with the nervous system with no direct participation of the sensory or the motor systems. Neural interfaces were first hypothesized in the early 60's to augment body functionalities in astronauts or pilots – the notion of cybernetic organism or ►cyborg. However, they became feasible with the progress in the technology of microelectrode arrays, which enabled the access to a neural system from multiple sites. Since then, they have become essential tools in the investigation of the dynamic and distributed nature of ►neural coding. Moreover, they have found an important area of application as aids for persons with sensory or motor disabilities.

There are two main types of neural interfaces: (i) brain-computer interfaces (BCIs), in which the activity of the nervous system is directly used to control external devices (computers, robots or prostheses); and (ii) neuroprostheses, in which physical devices are designed to induce spatio-temporal patterns of neural activity.

The aim of brain-computer interfaces is to use some measurement of the activity of the nervous system to control external devices, with no direct participation of peripheral nerves and muscles. More specifically, BCI technologies [4] use brain activity recorded

externally, i.e. on the scalp (►electroencephalography, EEG), or intra-cranially (epidural, sub-dural or intra-cortical), to control the movement of a cursor on a computer screen, or that of a robot.

Neuroprostheses aim at substituting for impaired sensory modalities, and always involve artificial replicas of the dysfunctional sensory receptors (or parts of them). Stimuli are applied to sensory nerves, thus mimicking the effect of natural sensory stimuli.

In BCIs, bi-directionality in the exchange of information is achieved through the sensory system (e.g., vision) that provides the brain informations on the outcome of the generated action. In neuroprostheses, bi-directionality is provided by the actions generated in response to the simulated sensory stimuli. Both types of neural interface require substantial training to allow subjects to either generate the correct action or correctly interpret sensor stimuli. Bi-directionality is essential to such training phase.

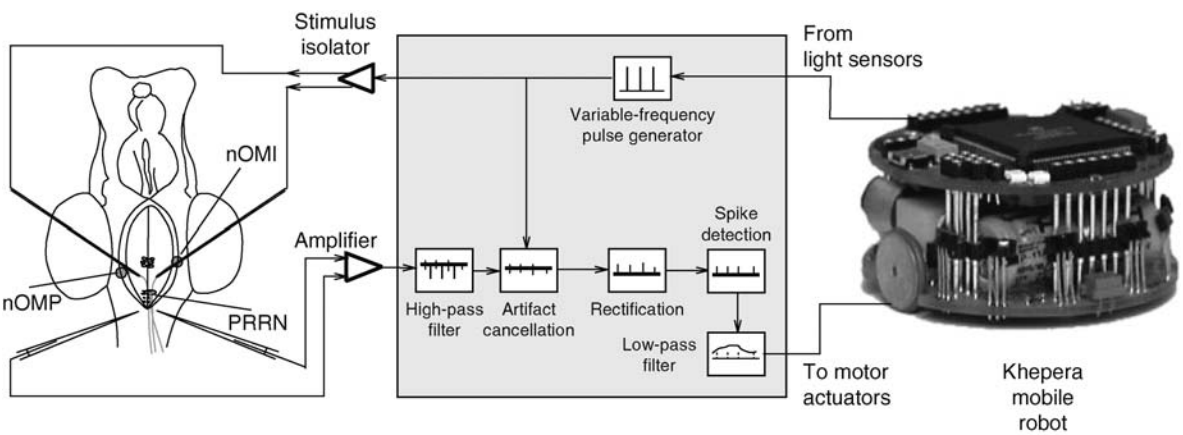
Embodied neural systems are a special class of computer-neural hybrids (Fig. 4), in which portions of nervous tissue are connected to either a "virtual," computer-simulated [5], or a physical [6] body, equipped with sensors and actuators, thus forming an artificial/hybrid ►autonomous system. In these artefacts, also referred as hybrots or neurally controlled ►animats, artificial sensory and motor systems allow the neural system to interact with the external world.

Function

In neuroscience research, computer-neural hybrids can be seen as a method of investigation of complex neural systems, which falls midway between cellular and population electrophysiology experiments and simulations based on ►computational models. In a modeling approach, one wants to investigate the effect of a specific component (a conductance, a synapse, a population of neurons, a sensory or motor system or even the whole body) on the whole neural system. However, while we may be able to model that specific component accurately, this may not be the case for the remaining parts of the system. The computer-neural hybrid method consists of replacing the well-modeled part with a computer-simulated computational model, in which all the details are under control, including the interaction with the external world. The model is then allowed to interact with the actual neural system, with all its complexity intact and the possibility of further manipulations. This experimental paradigm may potentially allow manipulations of the neural system under study that once were only possible with simulations on detailed, large scale computational models.

Dynamic clamp is now a well established technique in modern electrophysiology. It has been initially applied to the simulation of membrane ►conductances in single neurons. In this way, it is possible to observe the interaction between the added and the existing conductances, and compare the effect of simulated and actual conductances. Conductances may also be subtracted, i.e. it is possible to simulate negative conductances that cancel out existing ones.

The same technique may be used to simulate synaptic conductances between neurons. The current injected into a neuron can be made dependent on the membrane potential of a different neuron, as if there were a synapse among them. In this way, it is possible to investigate, for instance, the effect of the strength of the artificial synapse on the dynamic behavior of the hybrid neural circuit. An extension of this idea is to construct hybrid circuits that are made of both artificial and actual



Computer-Neural Hybrids. Figure 4 Example of an embodied computer-neural hybrid. The (multi-site) electrical activity of is recorded and decoded into a "motor command" which is used to control the artificial actuators. At the same time, the activity of the artificial sensors is coded into a set of stimuli that are delivered to the preparation through a stimulus isolator. The example refers to an experiment [5] in which the brainstem of a sea lamprey was connected to a small mobile robot.

neurons. For instance, hybrid combinations of biological and artificial neurons have been used to study and replicate a circuit involving retinal ganglion cells, ►reticular formation interneurons and thalamocortical neurons. Manipulation of the strength of the inhibitory synapse between the reticular interneuron and the thalamocortical neurons allowed to regulate the correlation between sensory input and thalamic activity, including the functional disconnection observed during sleep. Another example of application of dynamic clamp is the simulation of in-vivo synaptic inputs in an in-vitro slice preparation.

In computer-neural hybrids at population level, the same approach is extended to entire neural populations. Again, the artificial part of the hybrid provides a well-modeled environment for the neural system. For instance, a computer was used to control the dynamic regime of populations of ►culture of neurons [7] in closed-loop, and to induce a transition from synchronized bursting activity into a more sparse spiking behavior, similar to *in-vivo* awake cortical dynamics. Another application demonstrated the feasibility of "teaching" cultured neurons to reproduce a desired, target population activity [8].

BCIs have been investigated mainly as aids to patients with severe neuromuscular impairments (e.g., amyotrophic lateral sclerosis or ►spinal cord injury), but could in principle be used in different contexts. The key element in a BCI is a decoding algorithm, which converts the raw electrophysiological signal into an output that is suitable for controlling the external device. Most EEG-based BCIs require a prolonged learning phase to train subjects to "encode" the desired action into observable changes in their measured neural activity. For instance, subjects may be trained to control the amplitude of their μ- or β-rhythms (portions of the EEG signal whose power spectrum is, respectively, in the 8–12 Hz and 18–25 Hz range), to control a cursor on a computer screen in one or two dimensions. State-of-art EEG-based BCIs have been estimated to have a maximum information transfer rate of 5–25 bit/min. Critical elements are the selection of the "relevant" features in the neural signal, i.e. the ones which allow the best selection/discrimination of the different actions, and the psychophysical and cognitive factors that affect the rate of learning for a particular application.

In intra-cortical BCIs, the neural activity of populations of cells in the motor areas of the brain cortex is recorded by means of chronically implanted ►microelectrode arrays (MEA), and has been shown to be usable for predicting the intended movement and even to control a robot arm in real-time. In particular, the signals recorded from a population of neurons in the rat motor cortex were used to drive a mechanical lever which controlled the release of a food reward [9]. The same cortical activity observed when a movement of the paw obtained the reward could also be maintained when the same reward was obtained by a movement of the mechanism and with the paw at rest. In experiments with monkeys [10], signals recorded from different motor areas have been demonstrated to predict the intended movement and of mimicking it by means of a robotic arm. Recently, intra-cortical BCIs have been experimented in restoring motor functions in human subjects.

As regards neuroprostheses, the existing implementations range in scope from experimental trials with single individuals, to commercially available devices. ►Cochlear implants are the best known examples of sensory prostheses. Widely used as aids for completely deaf patients, they consist of multi-channel electrodes, implanted in the internal ear and connected to an external processor, which translates and codes sounds into electrical pulse patterns. A similar but much more ambitious family of devices is that of ►retinal implants, for which clinical experimentation is just beginning.

The rationale underlying embodied neural systems is that the dynamic and adaptive properties of neural systems can be understood by looking at their interaction with their external environment, in a bi-directional closed-loop. If such an external environment is artificial, the points of interaction are well determined and therefore the modalities and patterns of interaction are fully observable. Moreover, the environment itself can be manipulated, and the changes in dynamic behavior that result from changes in the environment provide useful information for understanding the neural systems themselves. For instance [6], a bi-directional connection between a ►mobile robot and a lamprey ►brainstem, kept alive in-vitro, was used to investigate the functioning of neurons in the reticular formation, to quantify the complexity of neural dynamics and to investigate the dynamics of adaptation. In a similar application [5], a culture of dissociated neurons was connected to a computer-simulated body. Although they are little more than proofs of concept, embodied neural systems may help understanding how the collective properties of living neurons lead to learning, memory and the coding and processing of information, up to higher-level cognition and "intelligent" behavior.

The technologies enabling the interfacing of parts of the nervous system with artificial devices – electrodes, dedicated hardware for stimulation and recording – will open the way to entirely new approaches for investigating the brain and ultimately interacting with it therapeutically and/or prosthetically. Next-generation neuroprostheses, characterized by massive, possibly bi-directional interaction with the nervous system, would greatly benefit from low-power interfaces that support higher rates of information transfer, and

allow stimulation and recording at multiple sites. Flexible, general interfacing frameworks, possibly base on ►neuromorphic device, will make the development of neuroprostheses cheaper, and more easily adaptable to the needs of individual users. Effective two-way interaction would also enable novel rehabilitation technologies, in which the recorded brain activity could be used to control the patterns of neural stimulation, thus inducing a reorganization of portions of the nervous system.

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Concentration Gradient

Definition

Denotes spatially distributed differences in the concentrations (parts per volume) of particles in solution.

►Membrane Potential - Basics

Concentration Invariance

Definition

Sensory systems can operate effectively over a very wide dynamic range of stimulus intensities. In the olfactory modality, the same odorant can be unambiguously recognized as the same perceptual entity over a broad spectrum of concentrations, a phenomenon termed concentration invariance.

►Odor Coding

Concentric Contraction

Definition

A period of muscle activity during which the length of the muscle fibers decreases.

►Energy/Energetics

Concept

Definition

Concept (or category) is a discrimination in which stimuli belonging to one concept are discriminated from other stimuli belonging to other concept. In other words, concept discrimination is generalization among all stimuli within a category and discrimination between the categories.

►Discrimination

Concepts in Thinking

Definition

Concepts are the representations that are employed in thinking. Concepts are supposed to be recombinable to a large extent, which accounts for the productivity and systematicity of thought.

►The Knowledge Argument

Conceptual Analysis

Definition

A conceptual analysis in a narrow sense is an investigation into the use of a concept word (for example "knowledge") with the aim of finding (individually) necessary and (jointly) sufficient application conditions of that word. In a wider sense any investigation aiming at the clarification of a concept can be called a conceptual analysis.

►Knowledge

Conceptual Role Semantics

Definition

Conceptual role semantics (CRS), also called functional or inferential role semantics, claims that the meaning of a mental representation is its role in the cognitive economy of the agent, e.g. in perception, thought and decision-making. CRS is a version of the use theory of meaning, which holds that the way expressions are related to one another determines what they mean. The central idea is that the conceptual role of a particular representation is a matter of its causal relations to other states in reasoning and deliberation, and the way the expression combines and interacts with other representations to mediate between sensory inputs and behavioral outputs. It is associated with the functionalist approach to the mind, which characterizes mental states and their contents by their relations to sensory stimuli in terms of their causal interactions with input from the environment, other mental states and behavioral output.

►Theory Theory (Simulation Theory, Theory of Mind)

Conceptualization

Definition

Learning or understanding of abstract relations (e.g. more/less, same/different) to form categories, also termed "conceptual categorization".

►Cognitive Elements in Animal Behavior

Concha

Definition

The bowl-shaped portion of the outer ear.

►Hearing Aids

Concrete Entity

Definition

Something that exists in space and time; a particular thing, e.g. a particular stone or horse.

►Possible World

Concussion (Concussio Cerebri)

Definition

Immediate but transient loss of consciousness due to a blunt impact on the skull or decelerating and accelerating of the brain within the skull. Mild symptoms are "star-struck" dazedness and brief ►amnesia. More sever symptoms include faintness with hypotension, facial pallor, bradycardia, slow pupillary reaction or, at times, brief convulsions.

Condensation

Definition

Areas of a propagating sound pressure wave of maximal increased pressure (increase above the static pressure).

►Acoustics

Conditional Burster

Definition

A neuron that can generate rhythmic bursting activity in response to an excitatory input, but can only do so under the influence of a specific neuromodulator. Neurons

with endogenous bursting properties have a set of voltage-gated ion channels that enable them to produce oscillations of the membrane potential (i.e. alternating depolarizations and hyperpolarizations), which can drive bursts of action potentials.

However, in conditional bursters whilst these ion channels are present, they can not be activated sufficiently to generate membrane potential oscillations. The appropriate neuromodulator can enhance the function of these voltage-gated ion channels, so that they are able to respond with oscillations of the membrane potential in response to a prolonged excitatory drive.

►Central Pattern Generator
►Endogenous Burster

Conditional Knockout

►Conditional Transgenics

Conditional Overexpression

►Conditional Transgenics

Conditional Pacemaker Neuron

Definition

A neuron that generates pacemaker activity only in the presence of a neuromodulator.

►Bursting Pacemakers
►Conditional Burster
►Respiratory Pacemakers

Conditional Place Avoidance (CPA)

Definition

Animals learn to avoid a compartment or location that was previously paired with a noxious stimulus.

►Emotional/Affective Aspects of Pain

Conditional Somatic Deletion

►Conditional Transgenics

Conditional Transgenics

Fiona Mansergh
Ocular Genetic Unit, Smurfit Institute of Genetics, Trinity College Dublin, Dublin 2, Ireland

Synonyms

Conditional knockout; Conditional overexpression; Conditional somatic deletion; Recombinase mediated somatic cell mutagenesis; Tetracycline regulated transgenics

Definition

Transgenesis refers to the genetic modification of an organism via the introduction of foreign or mutated DNA construct(s) not present in the ►wild type of the species. A conditional transgenic is a genetically modified organism (GMO) in which the ►transgene can be overexpressed, downregulated or deleted, depending on the presence (or absence) of an enzyme, pharmaceutical or hormonal analogue. In other words, a conditional transgenic contains a mutated gene that can be turned on or off, often in an organ specific fashion, depending on the needs of the investigator.

Characteristics

Transgenic Mice

The first mammalian transgenics involved the introduction of non-native genes via injection of a DNA construct into fertilized mouse oocytes. However, this technology only permitted the addition of genetic material. Moreover, when using the same construct to generate different lines of transgenic mice, it became apparent that expression levels of the transgene could vary wildly. Depending on the genomic location into which the transgene integrated, its expression could be partially or wholly silenced. An advance on this method came with the discovery of mouse ►embryonic stem cells (ES cells) [1].

The Basics of Homologous Recombination (Gene Targeting)

Methods of culturing ES cells and of genetically modifying them advanced quickly, leading to the development of ►homologous recombination, also

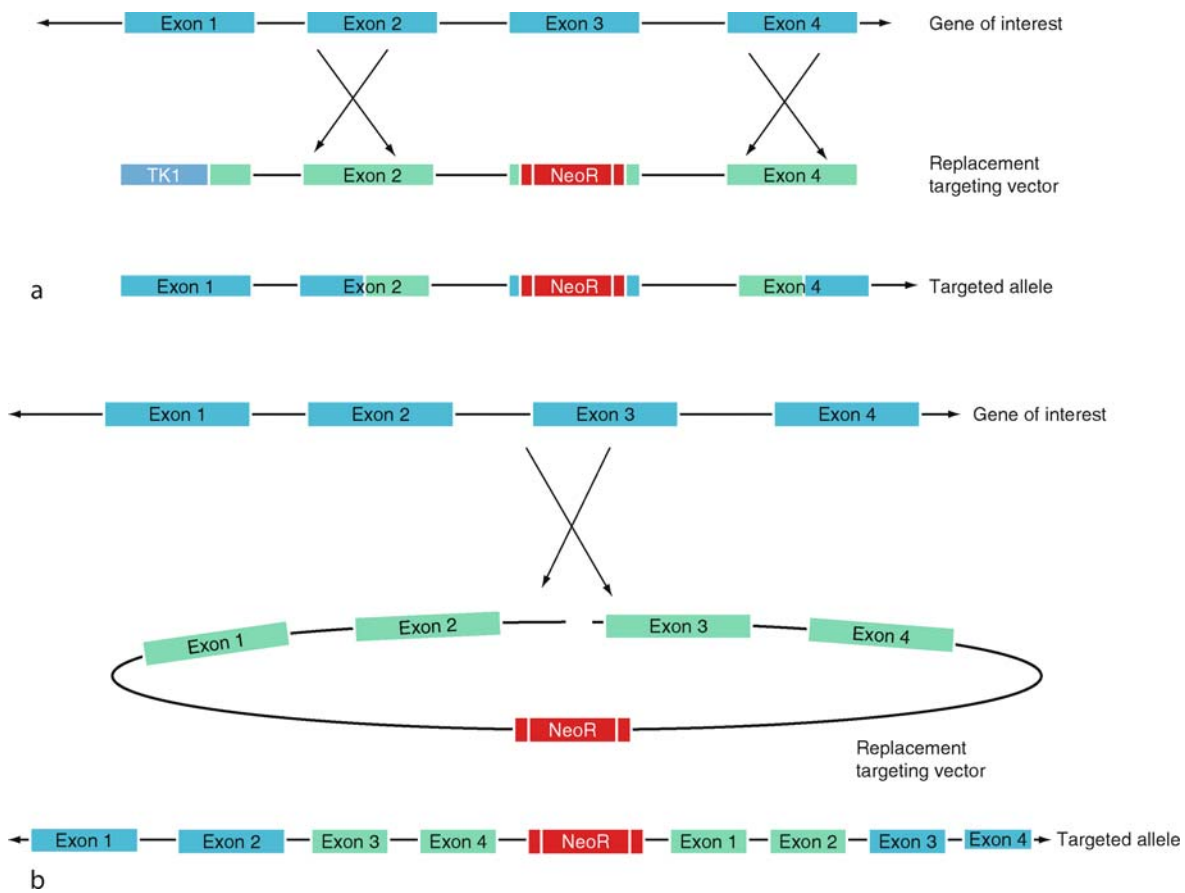
known as ►gene targeting [2]. Gene targeting relies on the cell's own capacity for recombination. ►Targeting vectors are generated, which contain homology to the gene that is to be modified, and one or more selection cassettes, which often encode resistance to a drug of choice (see Fig. 1).

Electroporation of targeting vector DNA results, in a small minority of cells, in a recombination event that integrates the targeting vector DNA into the gene of interest. This event results in ►heterozygous mutation of the gene of interest, incorporating drug resistance. Growth of electroporated cells in culture, using selection for drug resistance, should permit the growth of correctly targeted cells only. In practice, however, false positives usually outnumber targeted ES cell colonies and further screening (by long range ►PCR and/or ►Southern blot) is required in order to identify correctly targeted clones.

Targeted mice are then generated by injection of correctly targeted ES cells into mouse ►blastocysts or aggregation of the same cells with mouse ►morulae. Resultant hybrid embryos are inserted into the uteri of ►pseudopregnant female mice, and brought to term. ES cells are often derived from agouti (brown) 129 mice (the strain most permissive for the isolation of ES cells). Targeted ES cells are then aggregated with, or microinjected into, embryos derived from a strain with a different coat color (often black C57Bl6/J mice). Resulting offspring have cells derived from both the ES lineage (brown) and the C57Bl6/J embryos (black), are referred to as chimaeras, and are easily identifiable by their mixed coat color. In the event that the ES cells have contributed to the chimaeric ►germline, subsequent breeding of these animals with more C57Bl6/J mice will result in some brown offspring (agouti is dominant to black). These are ES derived and approximately 50% will transmit the targeted allele. Crossbreeding of this generation will result in mice homozygous for the mutant gene (unless the mutation is ►embryonic lethal).

The Need for Conditional Mutagenesis

Targeted mutagenesis has revolutionized biology; it has enabled us to study single gene function in mice by



Conditional Transgenics. Figure 1 Targeting vectors.

introducing precise mutations into the genome, in such a way that their expression in controlled. However, mutated genes are often embryonic lethal and recessive. This means that mice heterozygous for the targeted mutation are asymptomatic, while homozygotes do not survive gestation. While this demonstrates the essential function of that gene in a developmental process, it does not permit study of its function in later developmental events or in adults. This drawback led to the creation of various methods, whereby normal gene expression could be permitted during development, and then switched off in postnatal mice. Furthermore, modeling of disease can also require the overexpression of native genes, or of mutant versions thereof. Methods which can alter expression of a transgene in a temporally controlled and/or organ specific fashion are known collectively as conditional mutagenesis; mutant mice generated thereby are defined as conditional transgenics.

Conditional Genetic Deletion, Cre/LoxP Mediated Somatic Cell Mutagenesis

This method of conditional mutagenesis relies on the ability of certain recombinases to invert or delete segments of DNA via site directed recombination. Cre and Flp, derived from the P1 bacteriophage and Saccharomyces cerevisiae respectively, are most often used for this purpose. Lox P sites are specifically recognized by Cre, while Flp recognizes FRT sites. Both LoxP and FRT sequences are 34bp in length, incorporating two 13bp palindromes separated by an 8bp asymmetric core. DNA strand exchange between two LoxP or FRT sites is mediated by the relevant recombinase and depending on the orientation of the two sites with respect to each other and the number of DNA molecules involved, can result in deletion, insertion, duplication, integration or translocation of DNA sequences [3].

The ►Cre/LoxP system is by far the most commonly used, and so will be described in more detail below (Fig. 2).

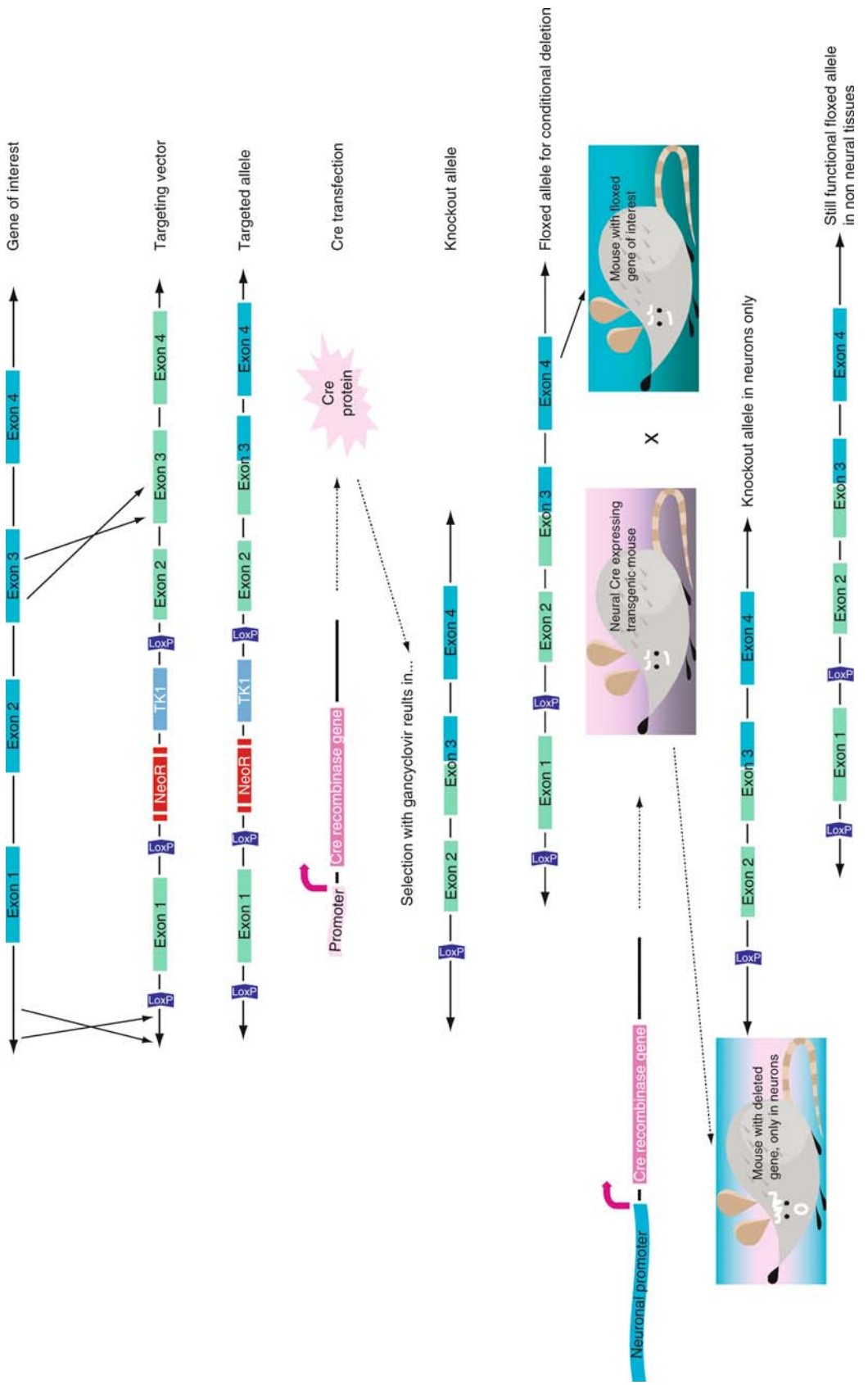
Conditional mutants are usually generated by introducing LoxP sites on either side of a vital exon of a gene of interest, via ►homologous recombination. When 2 LoxP sites are in cis (on the same DNA molecule) and in the same orientation (both 5′-3′ or both 3′-5′), their recognition by Cre will result in deletion of the DNA between the two sites. On their own, however, without Cre, these sites (in combination with an intronic selection cassette) should result in a normal phenotype, even in homozygotes. A second, transgenic mouse line can then be generated, which expresses Cre under a tissue specific and/or inducible promoter. Crossbreeding can then be used to generate mice homozygous for the LoxP modified gene and that express Cre in specific cell types or inducibly. The DNA between the LoxP sites is then deleted, either in a tissue/cell specific manner or inducibly, via administration of a drug. Transgenics expressing Cre under the control of various tissue specific promoters are catalogued at http://nagy.mshri.on.ca/cre/ (Gfap, synapsin, TH, mlc and En2 mice are available for neuronal Cre expression). Promoters that can be induced by specific pharmaceuticals (e.g., RU486, a progesterone analogue) can also be used to more finely tune the timing of somatic deletion.

Cre/LoxP can also be used to restore gene expression; where a gene has been inactivated by the insertion of LoxP sites, expression of Cre can reduce the number of LoxP sites to one, and remove inserted, mutagenic sequence. This has to be carefully designed such that the remaining LoxP site is neutral with regard to gene expression, and results in the expression of a normal protein however [4].

In addition to organ specific mutagenesis, this system has been used to generate stable germ line mutations and for large chromosomal deletions. In the first instance, the Cre system can be used to generate "cleaner" knockout mutations. Drug selection cassettes can contribute to phenotype and interfere with the interpretation of results. By surrounding the positive selection cassette with Lox P sites in the same orientation, selecting and screening for targeted cells normally and then electroporating a construct that transiently expresses Cre into the cells prior to chimera formation, the cassette can be deleted prior to creation of the knockout line. Targeted ES cell colonies can then be screened for the absence of the resistance cassette.

This technique has the disadvantage, however, that overexpression of Cre in ES cells can result in non-specific recombination, compromising germline transmission of the ES cells [5]. This problem has been neatly overcome by the development of elegant selection cassettes such as pACN, which contains not only a neomycin resistance (neoR) gene, but also Cre recombinase, under the control of a testis specific promoter. Targeted cell lines are selected for and screened in the normal way. Cre is then transiently expressed in the germline of male chimaeras, deleting the ACN construct and itself and thereby limiting the potential for chromosomal damage [6]. The final mutation is an 80+ basepair insertion containing one LoxP site and stop codons in all 3 frames.

A further use of Cre/LoxP technology has been to generate large scale chromosomal deletions. ►Loss of heterozygosity (LOH) has long been known to contribute to the pathogenesis of many forms of cancer, moreover, many mental retardation syndromes result from the loss (►Prader-Willi syndrome and ►Angelman syndrome) or duplication (►Down syndrome) of megabases of DNA. Deletions larger than approximately 30kb are now typically achieved by sequential targeting of two LoxP containing vectors with



Conditional Transgenics. Figure 2 Cre/LoxP.

different drug resistance on either side of the region to be deleted. This system has been adapted to the genomic era by Allan Bradley and colleagues at the Sanger centre, who have developed a series of paired insertion targeting vectors, the MICER resource, that map all over the genome ([7], http://www.sanger.ac.uk/PostGenomics/mousegenomics/). Use of one vector alone can be used for simple gene targeting, should it map within a coding region. Use of 5′ and 3′ vectors that map within a few Mb of each other can be used to generate large scale deletions, These vector pairs each contain a neoR or puroR cassette, and the 3′or 5′ half of an ►Hprt minigene; targeting is carried out sequentially in an Hprt −/− ES cell line, such as HM1 or AB2.2. Subsequent electroporation of a transient Cre can be used to mediate recombination between the LoxP sites in the two vectors, which, in the case of a deletion, will re-unite the two halves of Hprt. ►HAT selection can be used to isolate Hprt + colonies, some of which should contain the deletion of choice. This system could also be used conditionally, by crossing mice with the desired LoxP sites with those expressing a tissue specific Cre. Furthermore, use of 5′ and 3′ vectors on the same or different chromosomes could be used to model common disease causing inversions or translocations.

Disadvantages of Cre/LoxP (and Flp/Frt) include the fact that even the most tightly controlled of promoters can be less tissue specific (or biochemically inducible) than is strictly desirable, leading to low level Cre expression (and subsequent mutation), in tissues (or at times) other than intended. Furthermore, Cre driven mutation is often leaky, leading to a mosaic of cells, some of which contain the desired mutation and some of which do not. This has two consequences; firstly, the phenotype may be hypomorphic rather than null, secondly, in tissues that contain stem cells, undeleted stem cells may be selected to replace mutated cells that are possibly dying as a result of gene ablation. In this case, a transient phenotype may be followed by apparent recovery. Cre/loxP also relies on homologous recombination, which presently restricts its use to mice. Homologous recombination has been used to genetically modify bovine fibroblasts, followed by cloning, which has permitted the application of gene targeting to other animal species, holding out the possibility that the Cre/loxP system could be used for conditional mutagenesis. However, the handful of instances in which targeting has been used in sheep and cattle points to the fact that in most cases, technological complexity and cost may be prohibitive [8,9]. Finally, somatic cell deletion creates irreversible modifications to DNA, and is more useful in downregulating gene expression. Systems in which gene expression can be upregulated, or turned on and off repeatedly, are more useful under certain circumstances.

Inducible Conditional Gene Expression

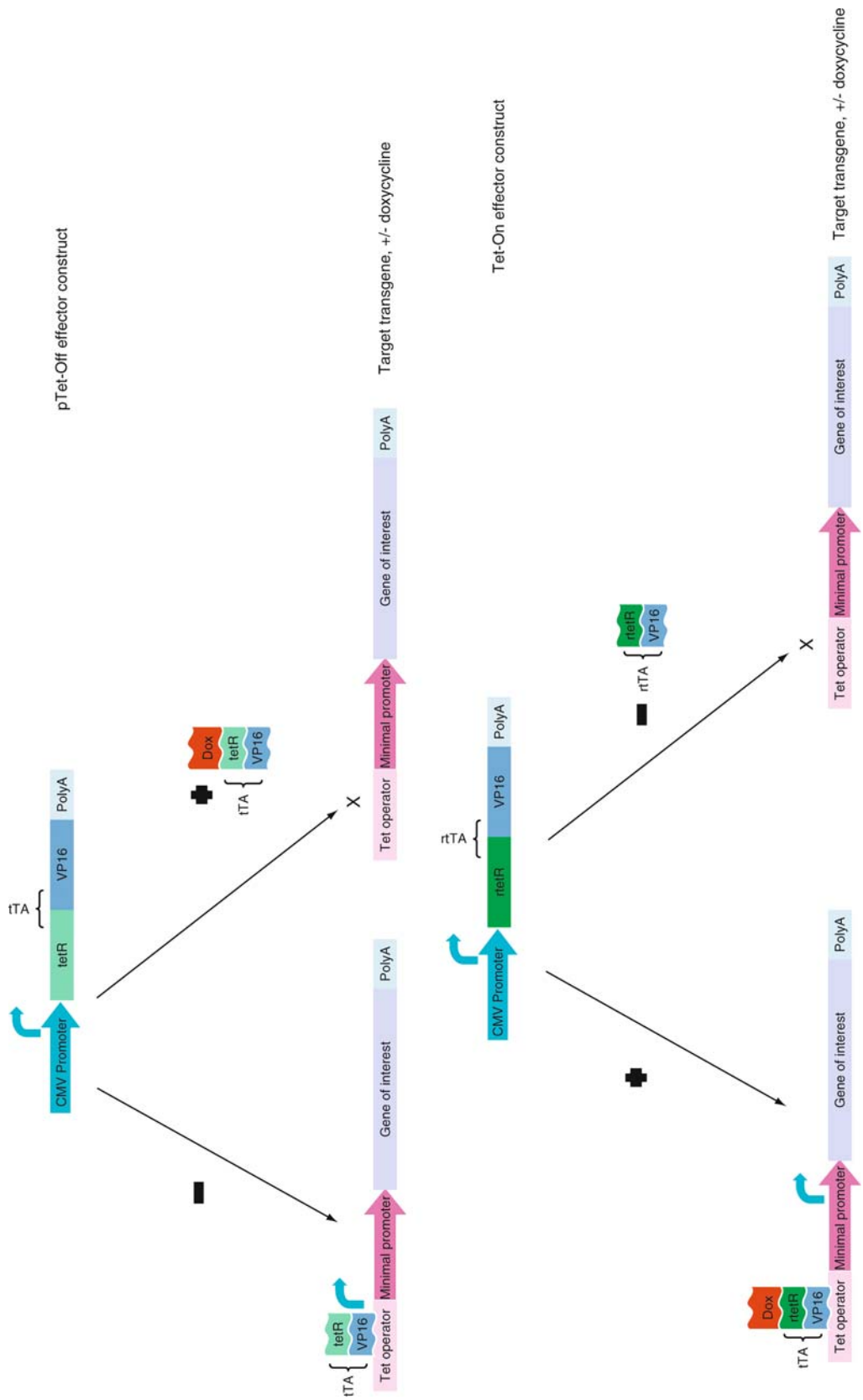
The tetracycline inducible system, known as Tet on/off, is the most commonly used inducible system (Fig. 3).

This system relies on manipulation of the control of tetracycline resistance gene expression, originally discovered in E. coli. The tetracycline resistance gene is constitutively repressed by the tetracycline repressor (tetR). This repressor binds to the tetracycline operator (tetO), a specific sequence in the tetracycline resistance gene promoter, which represses it. When tetracycline is present, it binds to tetR, which is then released from tetO, allowing expression of the tetracycline resistance gene.

This system has been modified for transgenic purposes. A CMV (cytomegalovirus) derived minimal promoter, fused with tetO sequences, is used to control gene expression. Meanwhile tetR has been fused with the activation domains of VP16 (an activator of herpes virus transcription). This results in a protein termed tTA (the tetracycline transcriptional activator), which activates tetO in the absence of tetracycline. Addition of tetracycline (or its analogues, doxycycline or anhydrotetracycline, which are less toxic), results in transcriptional repression, while gene expression can be turned on again once tetracycline has been cleared from the body. This system is known as tetOFF. Mutagenesis of tTA has resulted in reverse tTA (rtTA), which can only bind tetO in the presence of tetracycline (or analogues) and then activates transcription. In this case, addition of tetracycline activates transcription, while its removal results in downregulation (tetON) [3,10].

As with the Cre/LoxP system described above, using TetON/OFF systems in mice requires the crossbreeding of two strains, one carrying the transgene of interest, inserted downstream of the tetO/CMV promoter, and another carrying one of the tTA or rtTA genes (under the control of a tissue specific promoter, if required). Therefore, this system is extremely flexible; gene expression can be turned on or off upon multiple occasions, and can also, if desired, be restricted to certain organs or tissues. There are a number of disadvantages; leaky control of expression, toxicity or tetracycline insensitivity in certain cell types and unstable transcripts. Some tissues are more accessible to doxycycline than others; notably, doxycycline has limited access to the brain [4]. However, this system is highly accessible, owing to its commercial availability.

Similar inducible systems have been developed. One is based on induction of gene expression by ecdysone (which triggers insect metamorphosis), and also requires two lines of mice for activation. Another system uses the native Cyp1a1 enzyme promoter, which is induced by the administration of aryl hydrocarbons (such as indole-3-carbinol), and can be used to drive transgene expression [3]. This system has the advantage



Conditional Transgenics. Figure 3 TetOn/Off.

of only requiring one line of transgenic mice for induction, but has limited tissue specificity. All of these systems rely on transgenic methods, meaning that their application is not limited to mice. However, the downside is that variable transgene expression, depending on the location of insertion in the genome, can affect results. However, the use of insulator sites, which block interaction between cis acting regulatory elements and can be used to protect transgenes from positional effects, can hopefully be used to improve transcriptional consistency [4]. Alternatively, ►knock-in technology, where homologous recombination can be used to place a sequence of interest into a locus with a known expression pattern, can be used effectively.

In conclusion, various options exist by which one can finely tune the expression of both normal and mutant alleles (►Zygosity). These systems have different advantages and disadvantages, but are powerful methods by which gene function can be further elucidated.

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Conditioned Inhibition

Definition

This learning occurs when a stimulus (conditioned inhibitor) signals that the outcome (or US) will not occur. The procedure for establishing conditioned inhibition involves training one stimulus (A) as a signal for the outcome and simultaneously training a compound of that stimulus and another stimulus (AX) as a signal for no outcome. X acquires the ability to suppress or inhibit the conditioned response normally elicited by A. The presence of conditioned inhibition is further confirmed by showing that X will transfer its suppressive properties to another stimulus (B) that has been paired with the outcome (summation test) and will resist being trained as a signal for that outcome (retardation test). In these tests, the effect of X is compared to a control stimulus (Y) which was presented alone and with no outcome during conditioned inhibition training.

►Theory on Classical Conditioning

Conditioned Motivation

Definition

One of two mechanisms (the other being the enhancing function) by which reinforcers cause changes in future behavior.

►Neuroethological Aspects of Learning

Conditioned Reflexes

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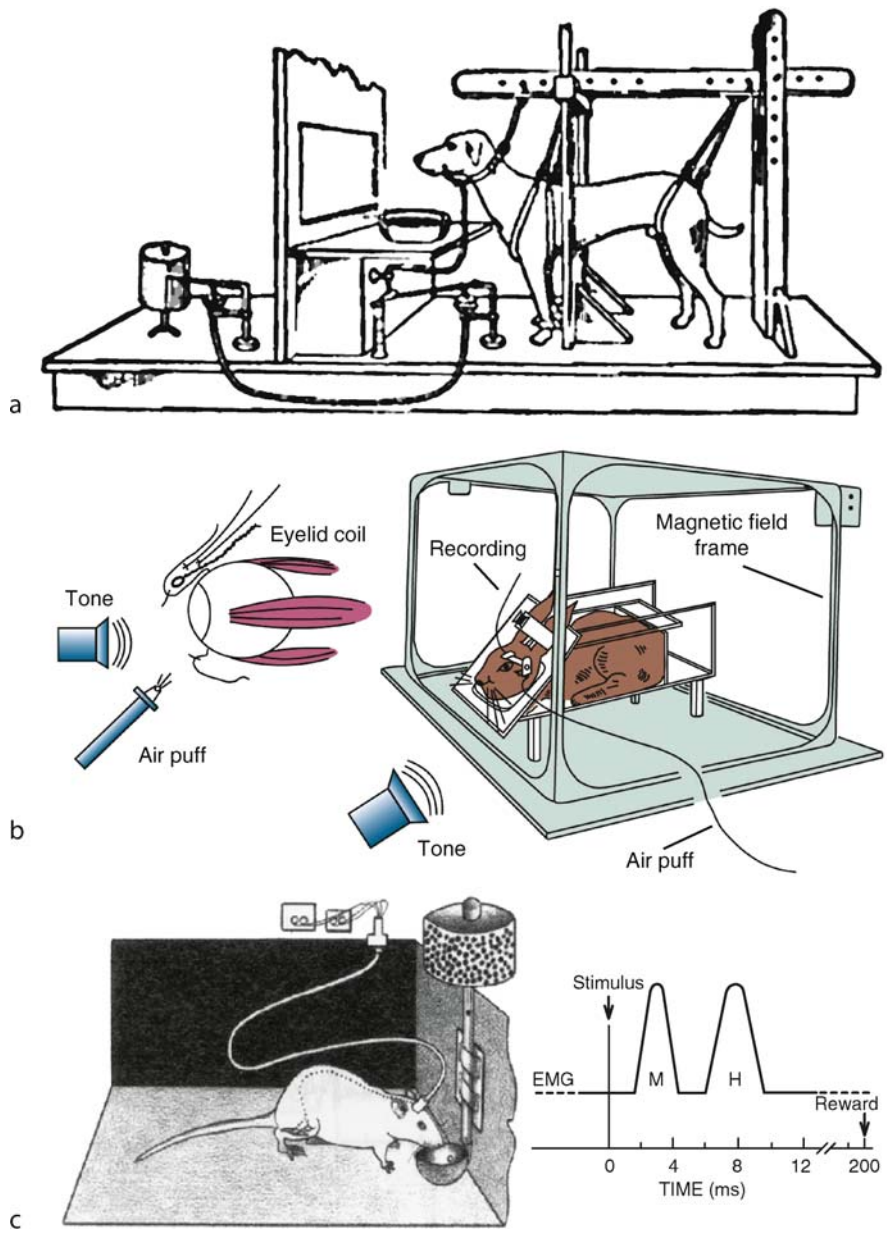
Definition

The word “reflex” is widely used in neuroscience and in psychology, as well as in every-day life, for different purposes and with different meanings. A definition that encompasses these different uses is: “A reflex is a behavior that reliably occurs at a characteristic latency



Conditioned Reflexes. Figure 1 (a) Classical conditioning of salivation in a dog. The apparatus shown is similar to that used by Pavlov to study conditioned salivary reflexes. First, food (the "unconditioned stimulus" or US) is repeatedly preceded by a sound (the "conditioned stimulus" of CS), and elicits salivation (the "unconditioned reflex" or US). Subsequently, delivery of the sound alone elicits salivation (the "conditioned reflex" or CR). Salivation is quantified by measuring flow rate in a capillary tube inserted in a salivary fistula. (From Yerkes RM, Morgulis S (1909) The method of Pawlow in animal psychology. Psychol Bull 6:257–273.) (b) Classical conditioning of eyelid closure in a rabbit. First, an air puff delivered to the cornea (the "unconditioned stimulus" or US) is repeatedly preceded by a tone (the "conditioned stimulus" or CS) and elicits eyelid closure (the "unconditioned reflex" or UR). Subsequently, the tone alone elicits eyelid closure (the "conditioned reflex" or CR). Eyelid closure is measured with a search-coil magnetic field technique. (From Delgado-Garcia JM, Gruart A (2006) Building new motor responses: eyelid conditioning revisited. TINS 29:330–338). (c) ►Operant conditioning of the H-reflex. Soleus EMG is monitored 24 h/day in a rat with chronically implanted electromyographic (EMG) electrodes and a tibial nerve cuff. The implant wires pass subcutaneously to a head-mounted connector and then through a flexible cable and a commutator to amplifiers and stimulator. The rat can move freely about the cage. Whenever the absolute value of soleus EMG stays in a specified range for a randomly varying 2.3–2.7 s period, a nerve-cuff stimulus elicits a threshold M response (i.e., a direct muscle response) and an H-reflex. For the first 10 days, the animal is exposed to the control mode, in which no reward

after a particular stimulus." Reflexes are typically (though not always) simple behaviors elicited by simple stimuli. Some well-known examples are the knee-jerk reflex, in which sudden muscle stretch causes the muscle to contract, the flexion withdrawal reflex in which a painful stimulus to the skin elicits rapid withdrawal, the pupillary reflex in which a flash of light causes the iris to contract, the salivary reflex in which the taste of food triggers salivation, and the startle reflex in which a loud sound elicits widespread muscle contraction.

These examples, and other reflexes typically present in normal animals or humans, are called " ►unconditioned reflexes (URs)." The stimulus that elicits a UR is called the "unconditioned stimulus (US)." In contrast, a " ►conditioned reflex (CR)" is a reflex that has been created or modified through a particular training, or "conditioning," experience. For example, a CR may be a behavior that is elicited by a stimulus that did not elicit it prior to the conditioning procedure. In this case, the newly effective stimulus is called a "conditioned stimulus (CS)."

Characteristics

Historically, CRs have been created by two different kinds of training experiences: "classical" or "Pavlovian" conditioning and "operant" or "instrumental" conditioning. In the past, intense interest in these procedures was motivated by the idea that all forms of learning and complex human behavior could be reduced to these elementary processes [1]. More recently, the prevailing view is that a more complex taxonomy is needed to encompass all forms of ►associative learning. For example, modifications of sensory cortex by experience may not be readily understood as either classical or operant conditioning. Nevertheless, researchers in the basic neurosciences continue to use them as valuable and tractable paradigms for exploring the biology of associative processes [2–4].

The traditional distinction between URs and CRs has also changed recently. In the past, URs were thought to reflect pre-determined patterns in the central nervous system. More recent views suggest that motor patterns arise through self-organization driven by complex interactions between genetic programs and environmental signals [5]. In association with these developments, the traditional sharp distinction between URs and CRs has broken down. It has come to be seen as a largely artificial distinction imposed by an experimenter (see below).

B. F. Skinner originally held that operant procedures applied to reflexes of the skeletal motor system and classical procedures applied to reflexes of the autonomic system. It is now clear that the same reflex can be modified by either procedure. The distinction between these two methods is procedural: operant conditioning involves the association of responses and reinforcement while ►classical conditioning involves the association of stimuli and reinforcement [6].

Classically Conditioned Reflexes

Classical conditioning originated in Russia with the work of Sechenov and Pavlov. In a classical conditioning procedure, the stimulus that is to become the CS occurs (or begins) just before a US. After repeated presentations of this CS/US pairing, the UR, which previously had been elicited only by the US, can be elicited by the CS alone. When it is so elicited by the CS, it is called a conditioned reflex, or CR. Pavlov conditioned dogs by arranging that the sound of a bell always proceeded application of meat powder to the mouth (Fig. 1a). Initially only the meat powder elicited salivation. After a number of such pairings, the dogs began to salivate to the sound of the bell alone.

Different subtypes of classical conditioning are distinguished by the exact relationships between the CS and the US, by whether the CR is an entirely new response to the CS, and/or by other features. Thus, in "delay conditioning" the US begins before the CS ends, while in "trace conditioning" the US does not begin until after the CS ends. In "α-conditioning" the CR is not an entirely new response to the CS, but is rather an intensification of a response that the CS elicited prior to conditioning. These and other specifics of conditioning procedures are described more fully in Mackintosh [6].

Of critical importance in considering classical conditioning phenomena is the distinction between actual conditioning and other changes in the relationships between stimuli and the responses they elicit. A true CR results only from the repeated pairing (or association) of a CS and a US. When random presentation of the US and CS, or of the CS alone, elicits a CR-like response, the phenomenon is called "pseudoconditioning," or "non-associative" conditioning.

In the years when conditioning was first defined and explored, there were attempts to interpret all or most

occurs and the H-reflex is simply measured to determine the size of the control reflex (the "unconditioned reflex" or UR). For the next 50 days, the rat is exposed to the up-conditioning or down-conditioning mode, in which a food-pellet reward is given if the H-reflex exceeds (up-mode) or falls below (down-mode) a criterion value. Background EMG and M response stay constant throughout. Successful conditioning (i.e., a change in H-reflex size of ≥20% in the rewarded direction) (a "conditioned reflex" or CR) develops in 75–80% of the rats (the others remain within 20% of control H-reflex size). (Modified from Wolpaw JR (1997) The complex structure of a simple memory. TINS 20:588–594.)

behaviors, even the most sophisticated human behaviors, as complex combinations of conditioned reflexes. Although such visions of conditioned reflexes as the basis of all behavior are no longer in fashion, experimental models based on conditioned reflexes play a prominent role in the increasingly reductionistic studies of the mechanisms of learning and memory.

These studies use a variety of different invertebrate and vertebrate models. Extensive studies in the marine snail, Aplysia, have clarified the cellular bases of classical conditioning. In the naive animal, a weak tactile stimulus (the CS) delivered to the siphon causes the gill to withdraw, while a painful stimulus (the US) delivered to the tail or head causes the gill to withdraw much more intensely (the UR). If the CS and the US are then paired repeatedly, the α form of classical conditioning results: the CS comes to elicit intense gill withdrawal (the CR). This conditioning involves plasticity at multiple sites in the central nervous system. Attention has focused on the synapse in the abdominal ganglion between sensory neurons and gill motor neurons. The CR is explained in part by activity-dependent presynaptic facilitation that is specific to the pathway that conveys the CS. The molecular mechanisms of both the short-term and long-term forms of this facilitation are complex, and the long-term form has been linked to changes in gene expression. Full expositions of current understanding of the mechanisms of this ostensibly simple learning are available [7].

Studies in vertebrate models have begun to reveal the specific contributions of different brain regions to classical conditioning. Models based on the eyeblink reflex are widely used. In a typical protocol, the CS is a tone and the US is an air puff to the eye that in the naive animal evokes an eyeblink (the UR) (Fig. 1b). After repeated pairing of the CS and US, the CS alone comes to evoke an eyeblink (the CR). The cerebellar cortex and the interpositus nuclei play key roles in the plasticity underlying development of this CR [8]. Other brain areas may contribute as well. The hippocampus is essential when a trace conditioning protocol is used.

Operantly Conditioned Reflexes

Operant conditioning originated in Britain and America with Bain, Morgan, and Thorndike [2,3]. In an operant conditioning procedure, the subject is presented with a particular stimulus or placed in a particular situation, and reinforcement, or reward, occurs when a particular response is made. After repeated exposures to this experience, the required response occurs more frequently and thereby increases the number of rewards. The neuronal and synaptic mechanisms of operant conditioning are likely to be even more complex than those now emerging from studies of classical conditioning. These mechanisms are being studied with model systems that use operant procedures to change simple reflexes.

The ▶H-reflex, the electrical analog of the "knee-jerk" reflex, is elicited by direct stimulation of sensory afferent fibers from the muscle spindle, which synapse in the spinal cord on the motoneurons serving the muscle and produce a contraction, the H-reflex. The H-reflex can be operantly conditioned: monkeys, humans, rats, and mice can increase or decrease it when reward is made contingent on its size (Fig. 1c) [9]. H-reflex change begins quickly and then continues at a much slower rate over days and weeks. The early change appears due to cortical influence on the spinal cord, while the gradual change reflects plasticity at multiple sites in the spinal cord that is gradually created by cortical influence. The cerebellum plays a key role. The spinal cord plasticity includes change in motoneuron firing threshold as well as in several synaptic populations. The H-reflex model is revealing how brain and spinal cord interact in a complex hierarchical fashion to produce operant conditioning of a simple reflex.

Model systems for studying the cellular basis of operant conditioning have been developed in several invertebrates. Comparisons of classical and operant conditioning in Aplysia have shown that the same biting reflex can be increased by either classical or instrumental conditioning. Furthermore, dopamine serves as the reinforcement transmitter in both forms [7]. Thus, the same neural circuits can be modified by both classical and operant conditioning. This suggests that similar mechanisms underlie both of these forms of associative learning.

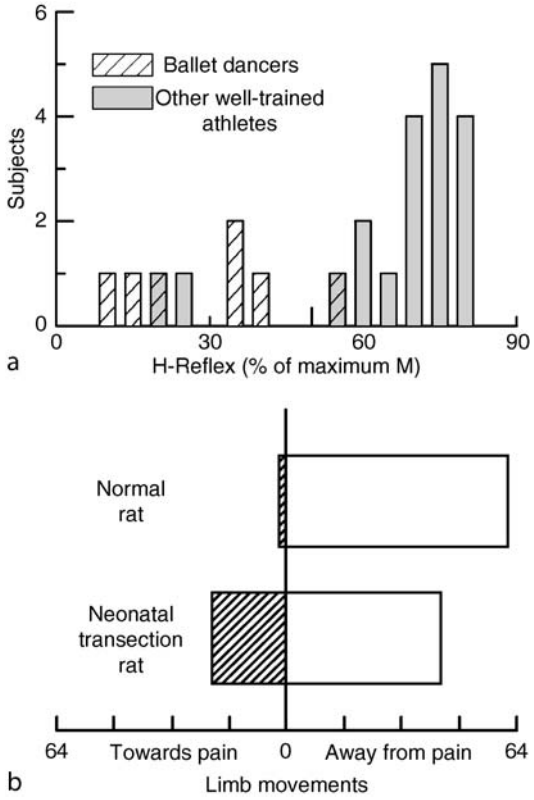
Reflex Conditioning is Important in Normal Life

Reflex conditioning is not limited to the laboratory. The concept of operant conditioning embraces phenomena produced by a wide variety of training experiences different from standard laboratory conditioning protocols. The gradual acquisition of any motor skill can be viewed as an operant conditioning procedure, in which improvements in performance serve as rewards that shape subsequent behavior. This process often includes changes in reflexes. The neuronal pathways responsible for reflexes such as the H-reflex participate in more complex behaviors, including standard motor skills such as posture and locomotion and the most sophisticated athletic and technical skills, as well as in the abnormal motor control associated with spinal cord injuries and other disorders [10]. Both laboratory and clinical studies indicate that reflex changes comparable to those produced by formal conditioning protocols occur as motor skills are acquired throughout life.

Spinally-mediated muscle stretch reflexes and ▶flexion withdrawal reflexes, which are poorly focused and often inappropriate in newborn infants, become appropriately

focused during early life (Fig. 2a). This development depends on normal descending control from the brain. Later in life, muscle stretch reflexes and H-reflexes change gradually during skill acquisition (Fig. 2b). Furthermore, reflex conditioning procedures might be used to help restore more effective function to people with spinal cord injuries or other severe impairments of motor function [9].

In sum, the reflex conditioning phenomena produced in the lab by classical and operant conditioning procedures are part of a broad spectrum of activity-dependent plasticity that plays an integral part in the acquisition and maintenance of motor skills throughout life and in the functional deficits and compensations seen with trauma or disease, and that might contribute to new methods for restoring function to the damaged nervous system.



Conditioned Reflexes. Figure 2 (a) Reflex conditioning associated with skill acquisition. Soleus H reflexes are much smaller in professional ballet dancers than in other well-trained athletes (e.g., runners, swimmers, cyclists). (H-reflexes of sedentary subjects fall in between.) It is likely that these reflex changes facilitate the precise cerebral control and the muscle co-contractions that are required in ballet. (Modified from Nielsen J, Crone C, Hultborn H (1993) H-reflexes are smaller in dancers from the Royal Danish Ballet than in well-trained athletes. Eur J Appl Physiol 66:116–121.) (b) Shaping of flexion withdrawal reflexes during development. Direction of limb movement produced by flexion withdrawal reflexes elicited by a nociceptive stimulus in normal adult rats and in adult rats that had undergone spinal cord transection just after birth. Direction is almost always appropriate, i.e., away from the stimulus, in normal adults, but is often inappropriate in transected adults. Neonatal transection prevents the normal shaping of flexion withdrawal reflexes that results from the interactions in the spinal cord of descending activity from the brain and peripheral sensory inputs from the limbs. (Modified from Levinsson A, Luo XL, Holmberg H, Schouenborg J (1999) Developmental tuning in a spinal nociceptive system: effects of neonatal spinalization. J Neurosci 19:10397–10403.)

All Reflexes are Probably to Some Degree Conditioned Reflexes

Finally, the fact that reflexes are affected by activity-dependent plasticity throughout life (and even in utero) implies that the traditional distinction between unconditioned and conditioned reflexes is merely an artificial distinction imposed by an experimenter. In reality, most and probably all reflexes are conditioned in the sense that they have been shaped by activity. Those traditionally designated as "unconditioned," such as the normal flexion withdrawal reflex that withdraws a limb from a painful stimulus, are reflexes that have undergone standard conditioning in the course of earlier life, and thus are similar in most normal individuals. In essence, "unconditioned reflexes" are simply reflexes that were conditioned before the experimenter began to observe them.

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Conditioned Response (CR)

Definition

In classical conditioning, the conditioned response (CR) is a response evoked with time by the conditioned stimulus after repetitive pairing with the unconditioned stimulus. The CR is similar to the response evoked by the unconditioned stimulus.

►Classical Conditioning (Pavlovian Conditioning)

Conditioned Stimulus (CS)

Definition

In classical conditioning, the conditioned stimulus (CS) is a neutral stimulus at first and come to evoke a response (conditioned response) similar to the response (unconditioned response) evoked by the stimulus (unconditioned stimulus) that has been repetitively paired with the CS.

►Classical Conditioning (Pavlovian Conditioning)
►Conditioned Taste Aversion

Conditioned Taste Aversion

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Synonyms

Taste learning; CTA

Definition

A kind of classical (Pavlovian) conditioning or association learning in which animals acquire an aversion to a tastant (conditioned stimulus, CS) that was followed by aversive internal symptoms induced by a toxic substance (unconditioned stimulus, US).

Conditioned taste aversion (CTA) is also a kind of fear learning to avoid subsequent intake of the "harmful" food by exhibiting aversive behavior to the taste of the food. Thus, CTA is a robust defense device protecting animals against repeated consumption of toxic food [1]. When saccharin is used as a CS, the sweet and palatable taste is treated as an aversive taste after CTA acquisition. The quality itself may not change, while the perceived intensity may be enhanced to facilitate detection of the harmful substance, and a hedonic shift from positive to negative occurs. CTA is encountered at all levels of evolution, with similar forms of food aversion learning found in vertebrate and invertebrate species.

Characteristics

In a typical paradigm to establish CTA in laboratory animals such as rats and mice, the animals mildly deprived of water are allowed to drink a novel palatable solution, e.g., 5 mM Na–saccharin as the CS for 20 min, followed soon by an intraperitoneal injection of 0.15 M LiCl (2% volume of the body weight), which is known to induce internal malaise as the US [2]. On the test day after 1-day recovery period, if the animals avoid ingesting the CS and/or show aversive reactivities to the reexposure to the CS, we can judge that the animals have acquired CTA to the CS.

CTA is a rapidly established and robust phenomenon and has the following characteristics that are not found in other forms of classical conditioning [3]: (i) robust CTA can be established after only one pairing of a CS that is followed by an US, (ii) successful CTA can develop after delays of as long as several hours between exposure to the CS and delivery of the US, and (iii) the association between the CS and the US can proceed under deep anesthesia.

CTA as a Tool in Taste Research

Since CTA is considered to involve functions of the higher nervous system, the formation of CTA can be utilized as a tool to assess the functions of the higher gustatory centers. For example, the localization of a suggested cortical taste area of rat and hamster by the electrophysiological and anatomical methods was verified behaviorally using this technique, i.e., lesions of the relevant area disrupted the formation of CTA.

After acquisition of CTA, the animals remember the taste of the CS to show aversive responses to the CS, and this aversion is generalized to other taste stimuli with the similar taste. Therefore, examination of the generalization of CTA is an efficient method for determining how mammals classify taste stimuli. It is demonstrated that rats and hamsters categorize taste stimuli into four types corresponding to the four basic taste qualities such as sweet, salty, sour, and bitter, and mice (C57BL strain) can categorize the taste of monosodium glutamate into the fifth type corresponding to umami in humans. Such a behavioral categorization is utilized to elucidate the validity of neural coding hypotheses of taste quality such as the across-neuron response pattern theory and labeled-line theory [4].

Neural Substrate of CTA

Electrophysiological, behavioral, pharmacological, and c-*fos* immunohistochemical studies have suggested brain regions responsible for the formation of CTA. A variety of brain regions including the parabrachial nucleus, amygdala, insular cortex, supramammillary nucleus, paraventricular thalamic nucleus, nucleus accumbens, and ventral pallidum are involved in different phases of CTA acquisition and expression. Concerning the role of amygdala, the enhanced taste sensitivity to facilitate detection of the CS may originate in the central nucleus of the amygdala (CeA), and the hedonic shift, from positive to negative, may originate in the basolateral nucleus of the amygdala (BLA) [5]. In accordance with this notion, although the previous studies have yielded inconsistent behavioral results, overall electrolytic or excitotoxic lesions show little, if any, involvement of the CeA in CTA, whereas the lesions of the BLA in many cases disrupted or attenuated CTA. The BLA may also play an important role in CS–US association and formation of fearful emotion, and this nucleus is suggested to be involved in neophobia requisite for CTA formation [6]. Recent studies have been demonstrating that the reward system including the ventral tegmental area, nucleus of accumbens, and ventral pallidum, which is known to play a mediating role in the rewarding effects of reward (e.g., drugs, food intake) also plays a role in CTA [5,7].

Although the hippocampus plays minor role in the acquisition of CTA, it has been suggested to mediate the effects seen in the aged animal. Rats show compromised effects (e.g., blocking and context learning), strengthened effects (e.g., long-delayed learning), and no effects (e.g., latent inhibition) with ageing. Many of these effects can be produced by hippocampal lesions, suggesting that changes in the hippocampus with ageing may mediate the effects seen in the aged animal [8].

Molecular Mechanism of CTA

With the advantage of the characteristics of CTA as described above, CTA has been chosen as a good model for the study of molecular and biochemical mechanisms of plasticity and learning. It is conceivable that the CS presentation induces the formation of a short-term taste memory and that it is this trace that associates with the malaise-inducing US. The activation of muscarinic and glutamate receptors in the insular cortex and amygdale is crucial during the acquisition of CTA. This activation might be modulated by other neurotransmitter systems including the noradrenergic system [9]. Inhibition of protein synthesis with anisomycin in the insular cortex before and during CTA disrupts long-term but not short-term taste memory, indicating that the formation of CTA has a protein-synthesis-dependent phase. Concerning the biochemical level of the long-term taste memory, CTA is associated with changes in the phosphorylated state of several proteins, including extracellular regulated kinase and the 2B subunit of the NMDA receptor [10].

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Conditioning

Definition

Conditioning is method to train animals. One type of conditioning is respondent conditioning (classical or Pavlovian conditioning), in which a conditioned stimulus (CS) is paired with an unconditioned stimulus (UCS), which elicits behavior called the respondent or unconditioned response (UR). By conditioning or pairing CS with UCS, the CS begins to elicit conditioned response (CR). The other type of conditioning is operant conditioning (or instrumental conditioning) in which the outcome (reinforcement or punishment) of the behavioral response (operant) modifies the operant. A typical operant chamber for a rat is a small box with lever(s) and a food pellet dispenser. When the rat presses the lever, the dispenser

provides a food pellet. As a result, the rat learns to emit the lever-press behavior (operant) to get the food.

►Classical Conditioning (Pavlovian Conditioning)
►Operant Conditioning (Instrumental Learning)

Conditioning Lesion

Definition

One of two injuries, usually with a short period of time in between. The second injury "builds" upon the first one, and, as a result, the growth activity of the injured nerve cell is amplified.

►Neuronal Changes in Axonal Degeneration and Regeneration

Conductance (Electrical)

Definition

Conductance (electrical) is the measure of the ability of an electric circuit to conduct electricity and is the reciprocal of electrical resistance.

►Cable Theory
►Action Potential
►Membrane Potential: Basics
►Ohm's Law

Conductance-based Model

Definition

A single-point neuron model taking into account ionic current flow through membrane channels of different types.

►Neural Networks

Conduction Aphasia

Definition

Also called Central Aphasia; Conduction aphasia results from lesions of the ►arcuate fasciculus, which connects ►Wernicke's area with ►Broca's area, and is characterized by a severe deficit in repetition of what is heard or read, despite normal auditory comprehension, verbal fluency (which may be paraphasic) and writing.

►Broca's Area
►Wernicke's Area

Conduction Velocity

Definition

Velocity of action potential propagation along a nerve or muscle fiber.

►Action Potential Propagation

Conductive Hearing Loss

Definition

Hearing loss due to pathology of the outer and/or middle ear.

►Hearing Aids

Cone

Definition

Photoreceptor specialized for daylight vision, color and high acuity.

►Evolution of the Visual System: Mammals – Color Vision and the Function of Parallel Visual Pathways in Primates
►Photoreceptors

Cone Opponent

Definition

Wavelength-selective property of neural responses or human performance, produced when functional input

from one cone type is inhibited or "opposed" by input from a different cone type. Cone opponent neurons are typically excited by some wavelengths of light in the visible spectrum and inhibited by others.

►Color Processing
►Photoreceptors
►Retinal Color Vision in Primates

Cone Pedicle

Definition

Complex synaptic terminal of a cone photoreceptor that makes synapses with cone bipolar and horizontal cells.

►Photoreceptors
►Inherited Retinal Degenrations
►Retinal Bipolar Cells

Cone Photoreceptor

Definition

Cone-shaped photoreceptor cells of the vertebrate retina responsible for color vision under bright light. Based on peak spectral sensitivity, human cone cells are of three types; short wavelengths of light (437 nm), medium wavelengths of light (533 nm) or long wavelengths of light (564 nm).

►Photoreceptors

Confabulations

Definition

Faked and wrong reports and tales based on memory gaps and wrong memories with subsequent misinterpretations and inventions may occur within the ►amnestic syndrome (►Wernicke-Korsakoff syndrome), and as a result of various brain damages (arteriosclerosis, ►progressive paralysis (loss of muscle strength), brain injuries, alcoholism, poisoning).

►Wernicke-Korsakoff Syndrome

Configural/Configurational

Definition

Both terms are used as synonyms for synthetic odor mixture qualities.

►Olfactory Information

Congenital Indifference to Pain

Definition

Nav1.7-related congenital inability to experience pain is a very rare, autosomal recessive trait. These patients do not produce functional Nav1.7 channels and do not experience pain from normally painful acts such as inserting sharp objects in their hands or after bone fracture, tongue and lip biting, or walking on hot surfaces (burning coal). Heterozygous parents are asymptomatic suggesting that loss of functional Nav1.7 on one allele does not lead to haploinsufficiency.

►Voltage-gated Sodium Channels: Multiple Roles in the Pathophysiology of Pain

Congenital Malformation

Definition

Anatomical disorders with which the patient is born. Some congenital disorders are inherited.

Congruent Taste and Smell

Definition

Taste and smell that fit well together. Taste and smell usually encountered together in food in daily life.

►Flavor

Conjugate Eye Movements

Definition

These rotate the lines of sight of both eyes by the same amount and in the same direction (pure version as

opposed to vergence). They result from an equal innervation of functionally yoked pairs of extraocular muscles (e.g., right abducens and left medial rectus) emanating from a common source (Hering's law) and can be saccadic or smooth in nature; during saccades the coupling is not rigid, though, causing transient changes in vergence.

►Hering's Law
►Oculomotor Control
►Saccade, Saccadic Eye Movement
►Vergence Movements

Conjunction Errors

Definition

A mixture of details from different experiences, fused in memory.

►Memory Distortion

Connectionism

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Synonyms

Artificial neural networks; Neural computation

Definition

Connectionist models are computer models loosely based on the principles of neural information processing [1–3]. These typically take the form of artificial neural network simulations that embody general principles such as inhibition and excitation within a distributed, parallel distributed processing (PDP) system. The key idea is that of collective computation; although the behavior of the individual units in the network is simple, the behavior of the network as a whole can be very complex. They remain high-level information processing models and are not intended to model the functioning of individual neurons. They are intended to strike the balance between importing some of the key ideas from the neurosciences while maintaining sufficiently discrete and definable components to allow questions about behavior to be formulated in terms of a high-level cognitive computational framework.

Characteristics

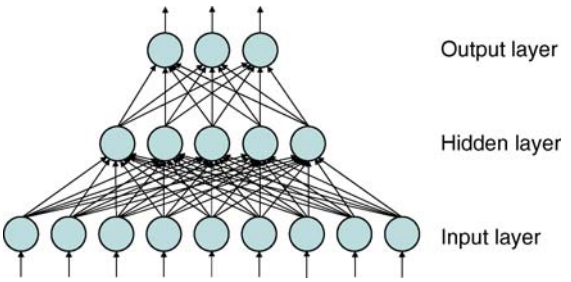
The History of Connectionism

McCulloch and Pitts first proposed in 1943 that networks of simple neuron-like processing units could compute logical functions. Later, Hebb's theories of associative neural learning provided the basis for implementing learning in such artificial neural networks. The main concept behind this form of learning is that the connection between two units is strengthened according to the frequency with which both units are co-active. In the late 1950s, Rosenblatt developed the first neurocomputer (called a ►perceptron) consisting of a simple neural network with a simple input and output layer. However, in 1969 Minsky and Papert [4] revealed that such networks were severely limited and could only compute linearly separable functions. In the late 1970s and early 80s new interest in the field was raised by the establishment of new, powerful learning algorithms for more complex models. These include the work by Hopfield, equating learning in connectionist nets to physical energy models, as well as Kohonen, who established models of self-organization. Another milestone of connectionist modelling research around that time was the emergence from the PDP (Parallel Distributed Processing) Research Group around Rumelhart and McClelland [1] who applied neural network principles to the understanding of cognitive functions. The discovery of the ►backpropagation learning algorithm allowed multilayered networks to be trained and enabled an escape from the limitations previously raised by Minsky and Papert. A more detailed historical perspective can be found in [5].

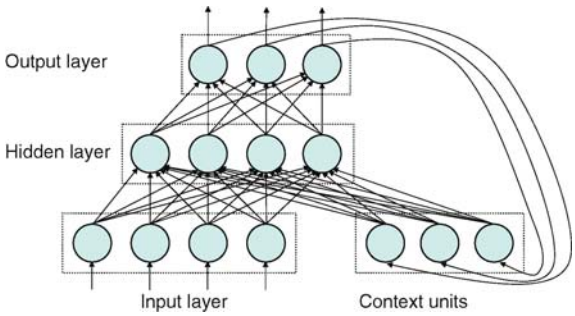
Processing Principles in Connectionist Models

Connectionist models consist of a number of simple processing units with weighted connections between them, similar to an idealized network of neurons. Activation flows from unit to unit via the connections. A unit becomes active when the activation flowing into it is either larger than a threshold value or when it falls within a certain range. Typically, activation is taken to represent the average firing rate of the unit and processing proceeds through discrete time steps in which the activation of all units is updated. However, some networks incorporate real-time dynamics into their models. In such cases, unit activation is computed according to a differential equation relating the change in activation level of a specific unit to its net incoming activation and any loss of signal that naturally occurs over time. Such real-time units are sometimes called ►leaky integrate and fire units.

Learning consists in adjusting the weights of the connections between the units. In *feedforward* networks



Connectionism. Figure 1 A fully connected feedforward network with three layers of units: nine input units, four hidden and three output units. All connections (indicated by *arrows*) lead from lower to higher layers.



Connectionism. Figure 2 A recurrent network: the hidden units receive input from both the input layer and the context nodes, which represent the output from previous steps.

(Fig. 1), information is first encoded as a pattern of activation across the bank of input units.

That activation then filters up through a first layer of weights until it produces a pattern of activation across the band of hidden units. The pattern of activation produced across the hidden units constitutes an internal re-representation of the information originally presented to the network. The activation at the hidden units continues to flow through the network until it reaches the output layer. The pattern of activation produced at the output units is taken as the network's response to the initial input. *Recurrent* networks allow information to flow backwards such that later stages of processing feedback to influence ongoing lower levels of processing. The introduction of recurrent, feedback connections implements a form of memory that enables the network to process temporal information [6] such as that necessary to process language (Fig. 2).

Learning in Connectionist Networks

There are four basic modes of training a connectionist network. In ►supervised learning, an external teaching signal is provided. The network gradually learns to associate a given input with this teaching signal by computing the discrepancy between its output and the teaching signal and adjusting the connection weights so as to minimize this discrepancy. The most frequently used algorithm for multilayer feedforward networks is backpropagation [1]. In this procedure, the sum of squared difference (output error) between a desired output (obtained from the teaching signal) and the actual output produced is propagated backwards through the net so that the weights of those connections that do not lead directly to the output layer can be adjusted appropriately. Because there is little biological evidence in support of error backpropagation, recent algorithms have tried to implement more biologically plausible forms of supervised learning. In ►unsupervised learning there is no teaching signal, and the task of the network is often to detect similarities between different inputs or to cluster the input data. Weights are adjusted until some internal constraint is satisfied. Kohonen maps, or self-organizing maps (SOMs), are common examples of unsupervised networks (Fig. 3).

In *reinforcement learning* there is no direct teaching signal but only feedback (reward) about the success of a task performed by the network. Finally, *self-supervised learning* is similar to supervised learning, but here the teaching signal is generated by the network itself rather than being external.

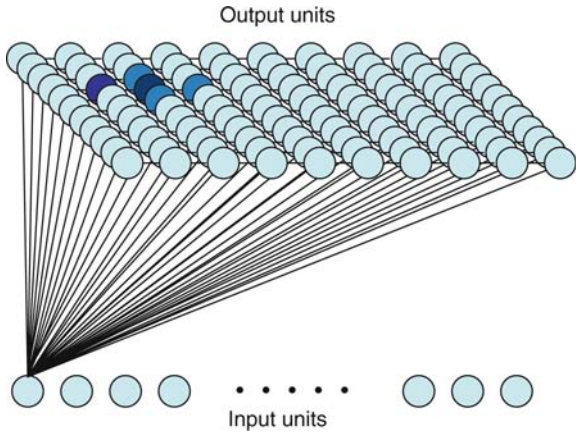
Constructivist Connectionist models

One extension to the classical PDP model architecture is to let the network grow its own architecture as it learns. So-called "constructivist" networks start out with a very small number of units. This minimal network is trained until performance no longer improves. Once this point is reached, the existing architecture is adapted by adding new units and connections, or in some cases pruning existing structures. Cascade Correlation, illustrated in Fig. 4, is a wide-spread variant of this constructivist paradigm.

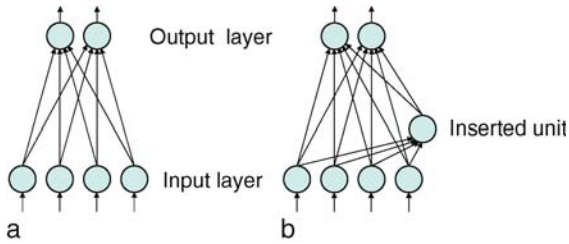
Such networks are particularly good at modelling cognitive development, in which the gradual accrual of cognitive capacity is an integral part of development [7]. In such models, the growing of new processing units is not taken to correspond to neurogenesis, but is interpreted at a more abstract level as relating to the construction of a network structure on the basis of adaptive learning.

Examples of Connectionist Models

Connectionist models have had most impact in the domains of language (where they challenged traditional notions of Chomskyan linguistics) and cognitive development (where they provided tangible process models for how development could occur). Perhaps the most well-studied example of such models is in the acquisition of the English past tense. Regular English verbs can be put in the past tense by adding the suffix "-ed" to the end of a verb root, while irregular past tense forms are constructed in a different way. The pattern of



Connectionism. Figure 3 Unsupervised learning: in self-organizing maps, an active unit partly distributes its activation to its neighbors. Eventually clusters of units emerge, representing a topological map of the input.



Connectionism. Figure 4 A constructivist network: (a) the first stage, with the original set of only input and output units, (b) after inserting an additional unit.

errors observed in children learning the past tense had lead researchers to argue that the past tense was acquired through the formation of morphological rules. A series of connectionist simulations [1,2] showed that rule following was an emergent epiphenomenon and that learning in a parallel distributed system was a much more accurate reflection of how children learned the past tense.

Connectionist models have also been used to construct explanatory models of acquired disorders such as some forms of dyslexia [8]. Here connectionist models were trained to process written words and output their meaning. Once trained, they were damaged in different ways. Depending on where the damage occurred, the models reproduced error patterns observed in either deep dyslexics or surface dyslexics, suggesting that there was a single unified processing model that could account for a range of different reading disorders. More recently, connectionist models have also been used to explore the effects of damage occurring at different points during development on the ability to recover from a range of developmental disorders.

Limitations of Connectionist Models

Feedforward connectionist networks have been shown to be universal approximators in the sense that, given an unlimited number of units, for any continuous input–output function there exists a network topology that can approximate it. However, while such an architecture may exist, there is no guarantee that the learning algorithms used to train networks will be able to discover it. Thus, connectionist networks are not universal learners. Indeed, many of the problems associated with connectionist networks relate to learning. The first problem is common to all statistical learning procedures: given a certain set of training data, i.e., inputs with associated teaching signal, the network may learn to perform perfectly on these, but still fail to generalize to novel data. This is known as ►overfitting: the function learned by the network is too specific. Overfitting can generally be avoided by providing a sufficiently large training set, or by refraining from extensive amounts of training. *Error minimization* is a second problem specific to the training algorithm. Mathematically, ►gradient descent algorithms such as backpropagation attempt to find a set of connection weights such as to minimize the network's output error. Because they approach this minimum by making small, local changes to the overall setting of weights, this may result not in the global, but merely a local minimum of error (i.e., a partial solution that goes some way to solving the problem but is inconsistent with the full solution). In that case, network performance may fail to improve after some amount of training, despite the existence of a better setting. A third problem is ►catastrophic interference [9] in which a task currently being learned overwrites previous learning. As network weights are adjusted to improve performance on a new task, performance on a previous task that relied on the old set of weights decreases, often catastrophically.

One solution to the problem of catastrophic interference has been to propose a dual systems approach to knowledge accrual [10]. This approach posits that one function of *cortico-hippocampal interplay* is to overcome catastrophic interference in cortical neural networks. The neocortex is presumed to be a slow learning system with sensory input as well as indirect input via the hippocampus. The hippocampus is a fast learning system that develops internal representations over a much smaller time window from direct sensory input. It then provides a training signal used for gradual learning in the neocortex. Thus, although the hippocampal system is susceptible to catastrophic interference, learning in the neocortex is resistant to interference thanks to the gradual interleaved training signal coming from the hippocampal system.

Finally, connectionist models fail to capture the apparently systematic and compositional nature of conceptual and linguistic knowledge available to

human adults. Processing in connectionist networks is inherently context dependent. The meaning of any individual unit depends on the state of other units that may be active in the network at the same time. This does not appear to be the case in human conceptual systems in which elementary conceptual tokens can preserve their meaning over and above what other tokens may be present [2]. However, while representations in connectionist networks do not normally show compositionality and systematicity, it remains an open question whether human cognition really does.

Acknowledgements

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Connectionist Architecture

Definition

A cognitive system has a connectionist architecture if its cognitive processes or its intelligent behavior does not rely on structure-sensitive manipulations of symbols, but on the activity of parallel distributed neural networks.

►Representation (Mental)

C

Conscious Perception

Definition

The reportable content of perception. A sensory stimulus has a better chance of reaching consciousness when attention is focused on it. While most of our thoughts and actions are guided by conscious perception, unconscious perception may nonetheless affect the quality of human performance and emotion.

►Attention
►Perception

Consciousness, Intentional

Definition

A person has intentional consciousness when she is living through a mental episode that is characterized by a certain content, i.e. by something the episode is of or about. Perceptual episodes are of or about particulars, while thoughts have propositional contents (Propositional attitudes). Phenomenologists insist that intentional consciousness is intrinsically "directed" to objects (Phenomenology). Alternatively, mental states may have a content in virtue of extrinsic causal relations.

►Argument
►Logic

Consciousness, Phenomenal

Definition

A person has phenomenal consciousness when she is living through a mental episode that has a characteristic feel, which is called a quale (pl. qualia). Being in pain or

having the sensory experience of something red are kinds of such episodes. It is somehow for the person to be in pain, and a person who has never had that kind of [□] experience cannot know what it is like to have it – or so many philosophers think.

►Argument
►Logic

Consensual Light Reflex

Definition

When one eye is illuminated, the pupil of the contralateral eye also constricts. This occurs as a result of bilateral projections from the pretectal neurons to the ipsilateral and contralateral neurons of the Edinger–Westphal nucleus.

►Neural Regulation of the Pupil

Consensus Binding Motif

Definition

Specific DNA oligonucleotide sequences recognized by a class of transcription factors or other DNA binding proteins. These binding motifs are usually localized to proximal promoters, but may also be found in intronic sequences and distal promoters that regulate target gene expression.

Consensus Sequence

Definition

A consensus sequence is determined by comparing aligned DNA sequences by using bioinformatic computer programs and identifying conserved sequence motifs. Usually the consensus sequence is shown indicating those nucleotides that are highly conserved and invariant and those that are more variable.

Conservation Law

Definition

A balance law in a case for which there is no change in the content of the corresponding physical quantity (such as can be the case for the mass content of a material body).

►Mechanics

Consolidation of Motor Memory

Definition

Process during which fresh motor memories, which are prone to various forms of interference, become interference resistant and thus long-term. Memory consolidation usually occurs in a confined period (window) of time following training, and generally involves protein synthesis.

►Motor Learning

Conspecific

Definition

(adj) from the same species as the animal being studied. The term is used extensively in the field of animal communication to distinguish communication signals originating from animals of the same species with those originating from other species (heterospecific) or from environmental sources.

Constant Field Equation

Definition

Is another expression for the Goldman-Hodgkin-Katz equation

►Membrane Potential - Basics

Constant Internal Environment of an Organism

►Homeostasis

Constant "Milieu Intérieur"

►Homeostasis

Constant Routine (CR)

Definition

An experimental protocol designed to allow for the accurate assessment of the human circadian rhythm of core body temperature by controlling the effect of exogenous variables such as light, ambient temperature, sleep, and activity. Subjects remain in bed in a semi-recumbent posture in a climate controlled laboratory suite under low light conditions for one or more circadian cycles. Meals are replaced by frequent isocaloric snacks and sleep is postponed until the end of the procedure.

►Circadian Cycle
►Circadian Rhythm
►Masking (Positive/Negative)

Constitutive Law

Definition

The statement of the response of a particular material (in terms of quantities such as stress and heat flux) to the history of the motion (in terms of quantities such as deformation and temperature). The quantitative aspects of constitutive laws are expressed in terms of constitutive equations.

►Mechanics

Constitutive Route

Definition

Constitutive route refers to the passage of vesicles which move directly, without being stored, from the Golgi apparatus to the cell membrane.

►Salivary Secretion Control

Constitutive Theory

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Definition

The statement of the response of a particular material (in terms of quantities such as ►stress and heat ►flux) to the history of the motion (in terms of quantities such as ►deformation and temperature). The quantitative aspects of ►constitutive laws are expressed in terms of constitutive equations.

Description of the Theory

The ►kinematics of deformation and the ►balance laws of ►continuum mechanics (q.v.) apply to all ►material bodies, regardless of their physical constitution. They are equally valid for solids, liquids and gases of any kind. Even a cursory count of equations reveals that these laws are not sufficient to solve for all the fields involved. What is missing is a representation of the material response in a manner tailored to each material or class of materials. This tailoring is far from arbitrary. It must respect certain principles, the formulation of which is the aim of the constitutive theory.

If the *history* of a body is defined as its motion and its ►absolute temperature for all points of the body and for all past times up to and including the present, then the principles of *causality* and *determinism* assert that the history completely determines (by means of *constitutive functionals*) the present values of the stress tensor (**T** or **t**), the heat-flux vector (**Q** or **q**), the ►internal energy density (u) and the ►entropy density (s). It will be assumed (*principle of* ►*equipresence*) that the list of independent variables appearing in each of the functionals just mentioned is, a priori, the same. For example, if the temperature is a determining factor for the heat flux, then it should a priori be considered

determining for the stress as well. The theory of materials with memory (even fading memory) is beyond the scope of this article. Instead, only a few examples of classes of materials characterized by a dependence not on the whole history of the motion and the temperature but just on the present values of the ►deformation gradient, the temperature, its gradient and possibly their time derivatives will be presented. Moreover, it will be assumed that these materials are *local*, so that the fluxes and densities at a point depend only on the values of the independent variables (just listed) at that point. Even with these very restrictive assumptions (which, nevertheless, are general enough to encompass most material models in widespread use), it will be seen that the remaining two tenets of the constitutive theory, namely the *principle of* ►*material frame indifference* and the *principle of thermodynamic consistency*, are strong enough to impose severe restrictions upon the possible constitutive laws that might be measured in the laboratory. The general validity of the principle of material frame indifference and the particular methodology to implement thermodynamic consistency to be presented, have both been challenged on various grounds, which will not be discussed.

The Principle of Material Frame-Indifference

A change of frame (►see kinematics of deformation) has an effect on all observable quantities, such as deformation gradients, vorticities, temperature gradients and so on, the exact effect depending on the intrinsic or assumed nature of the quantity at hand. The principle of material frame indifference asserts that, although the independent and dependent variable of a given constitutive equation may be affected by a change of frame, the constitutive functions themselves are not affected, regardless of whether or not the frames are inertially related. In plain words, what the principle is stating is that material properties such as the stiffness of a spring, the heat conductivity of a substance or the coefficient of thermal expansion can be determined in any laboratory frame. Before this important principle can be applied to particular cases, it must be established once and for all how the measurements of some of the most common physical quantities change under a change of frame. The most primitive quantity is the spatial distance between two simultaneous events. By construction, the most general change of frame involves just orthogonal spatial transformations, whence it follows that all observers agree on the distance between two simultaneous events. A scalar quantity, the result of whose measurement is independent of the frame, is called a *frame-indifferent scalar*. On physical grounds (for example, by claiming that the length of the mercury line of a thermometer is the distance between two simultaneous events, or perhaps through a more sophisticated argument or assumption) it is established that the absolute temperature is a frame-indifferent scalar. Since observers agree on length, they must surely agree on volume and they certainly should agree on the "counting of particles", so it is reasonable to assume that mass density is a frame indifferent scalar. On similar grounds it will be agreed that internal energy density and entropy density are frame-indifferent scalars.

Moving now to vector quantities and starting with the oriented segment $\mathbf{d}$ joining two simultaneous events, two flashlights blinking together in the dark, as it were, a direct application of (17) of ►kinematics of deformation to the ends of the segment yields $\mathbf{d}^* = \mathbf{Qd}$. A vector that transforms in this manner is called a *frame indifferent vector*. The unit normal $\mathbf{n}$ to a spatial element of area is frame indifferent, since it can be thought of as an arrow of the type just described. The unit normal $\mathbf{N}$ to a referential element of area, however, is not frame indifferent, since as far as the reference ►configuration is concerned, a change of frame has no consequence whatsoever. The ►velocity and ►acceleration of a particle are clearly not frame-indifferent. Moving now to tensors, a frame-indifferent tensor must be defined as a linear transformation that takes frame-indifferent vectors into frame indifferent vectors. It follows from this criterion that a tensor $\mathbf{A}$ is frame-indifferent if it transforms according to the formula $\mathbf{A}^* = \mathbf{QAQ}^T$. Assuming that spatial forces are frame indifferent, it follows, according to the definition above (since spatial normals are also frame-indifferent) that the ►Cauchy stress $\mathbf{t}$ is a frame-indifferent tensor (►Cauchy's Theorem). The deformation gradient transforms according to the formula $\mathbf{F}^* = \mathbf{QF}$, which shows that the deformation gradient is not frame indifferent. Its determinant J, however, is a frame-indifferent scalar. The ►first Piola-Kirchhoff stress tensor $\mathbf{T}$ is not frame indifferent. It transforms according to $\mathbf{T}^* = \mathbf{QT}$. The ►velocity gradient $\mathbf{L}$ is not frame indifferent since $\mathbf{L}^* = \mathbf{QLQ}^T + \dot{\mathbf{Q}}\mathbf{Q}^T$. The principle of material frame indifference *does not* claim that the quantities involved in a constitutive law must be frame indifferent. Quite to the contrary, it affirms that, even though the quantities involved are in general not frame indifferent, nevertheless the constitutive functionals themselves are *invariant* under a change of frame.

As an example of the application of the principle of material frame indifference, consider ►elasticity. A material is said to be *elastic* if the stress at a point is a function of just the present value of the deformation gradient at that point, namely:

$$\mathbf{t} = \mathbf{f}(\mathbf{F}), \tag{1}$$

where $\mathbf{f}$ is a tensor-valued function. Leaving aside the other constitutive functions (such as the internal

energy), what restrictions if any does the principle of material frame-indifference impose on this constitutive law? According to this principle, in another frame:

$$\mathbf{t}^* = \mathbf{f}(\mathbf{F}^*), \tag{2}$$

identically for all nonsingular tensors $\mathbf{F}$. Note the conspicuous absence of a star for the function $\mathbf{f}$, which is the whole point of the principle of frame indifference. According to previous comments about the way $\mathbf{t}$ and $\mathbf{F}$ change under a change of frame:

$$\mathbf{Q}\,\mathbf{f}(\mathbf{F})\,\mathbf{Q}^T = \mathbf{f}(\mathbf{QF}), \tag{3}$$

an equation that the function $\mathbf{f}$ must satisfy identically for all non-singular $\mathbf{F}$ and all orthogonal $\mathbf{Q}$, certainly a severe restriction. To make this restriction more explicit, the ►polar decomposition theorem can be invoked (see kinematics of deformation) to write:

$$\mathbf{Q}\,\mathbf{f}(\mathbf{RU})\,\mathbf{Q}^T = \mathbf{f}(\mathbf{QRU}). \tag{4}$$

Since this is an identity, $\mathbf{Q} = \mathbf{R}^{\mathrm{T}}$ can be chosen (at each instant) and, rearranging some terms, yeilds:

$$\mathbf{t} = \mathbf{R}\,\mathbf{f}(\mathbf{U})\mathbf{R}^T. \tag{5}$$

This restriction means that the dependence of the Cauchy stress can be arbitrary as far as the ►strain part ($\mathbf{U}$) of the deformation gradient is concerned, but the dependence on the rotational part is canonical.

The Principle of Thermodynamic Consistency

The second law of thermodynamics is a restriction that Nature imposes on all observable phenomena; certain things simply cannot happen. The point of view adopted to ensure that those things that should not happen never come out as a solution of the equations of continuum mechanics, is the following. Any constitutive law for which, under any conceivable process, the ►Clausius-Duhem inequality might be violated, even instantaneously, will be excluded. In the classes of materials dealt with, this statement implies that the Clausius-Duhem inequality must hold true identically for any instantaneous combination of the independent variables and their space or time derivatives. The restrictions that are obtained from the principle of thermodynamic consistency for the case of *thermoelastic heat-conductors* will be explored. In this class of materials it is assumed, by definition, that the constitutive variables are functions of the deformation gradient, the temperature and the temperature gradient, namely (in the ►Lagrangian description):

$$T^{iI} = T^{iI}(F^i_J, \theta, \theta_{,J}), \tag{6}$$

$$Q^I = Q^I(F^i_J, \theta, \theta_{,J}), \tag{7}$$

$$s = s(F^i_J, \theta, \theta_{,J}), \tag{8}$$

$$\psi = \psi(F^i_J, \theta, \theta_{,J}), \tag{9}$$

using the notation of the balance laws. For convenience, the free energy ψ has been substituted for the internal energy u. Notice, by the way, an application of the principle of equipresence; exactly the same list of arguments has been assumed for all constitutive variables, letting thermodynamics indicate whether or not an argument should be excluded from a particular constitutive law. Equations (6)–(9) are plugged into (30) of balance laws, the chain rule is used and terms are grouped together to obtain the following result:

$$\left(\rho_0 \frac{\partial \psi}{\partial F^i_J} - T^J_i\right)\dot{F}^i_J + \rho_0\left(\frac{\partial \psi}{\partial \theta} + s\right)\dot{\theta} + \rho_0\left(\frac{\partial \psi}{\partial \theta_{,J}}\right)\dot{\theta}_{,J} + \frac{1}{\theta}Q^J\theta_{,J} \le 0, \tag{10}$$

where the fact that $v^i_J = \dot{F}^i_J$, by the symmetry of mixed partial derivatives is used. The inequality obtained should be valid identically for all values of $\dot{F}^i_J$, $\dot{\theta}$, $\theta_{,J}$ and $\dot{\theta}_{,J}$. But this inequality is *linear* in $\dot{F}^i_J$, $\dot{\theta}$ and $\dot{\theta}_{,J}$, since none of these variables appear, anywhere except as multipliers of other expressions. This is not the case for the variable $\theta_{,J}$, since the heat-flux vector that it multiplies may depend on it, according to the constitutive assumptions. Since a linear function cannot have a constant sign over its whole domain, it must be concluded that the identical satisfaction of the inequality demands the satisfaction of the following equations:

$$\rho_0 \frac{\partial \psi}{\partial F^i_J} = T^J_i \tag{11}$$

$$\frac{\partial \psi}{\partial \theta} = -s \tag{12}$$

$$\frac{\partial \psi}{\partial \theta_{,J}} = 0 \tag{13}$$

and the residual inequality:

$$Q^J\theta_{,J} \le 0 \tag{14}$$

These remarkable restrictions can be summarized as follows. The ►free energy (of Helmholtz) density is independent of the temperature gradient and acts as a potential for the stress and the entropy density, both of which are, consequently, also independent of the temperature gradient. Eleven of the constitutive functions of departure boil down therefore, to a single scalar function ψ. Moreover, according to the residual inequality, heat cannot flow from lower to higher temperatures, since the heat-flux vector cannot form an acute angle with the temperature gradient! If, for example Fourier's law of conduction, which establishes that the heat-flux vector is proportional to the temperature

gradient, is postulated it is concluded that the constant of proportionality must be negative. The coefficient of heat conduction for real materials is in fact defined as the negative of this constant, so as to be positive.

An interesting by-product of the example just presented is that if attention is restricted to processes of a thermoelastic heat conductor that take place at a strictly constant and uniform temperature throughout the body, the heat flux vanishes identically, the processes are reversible and the first Piola-Kirchhoff stress is derivable from the free-energy function per unit referential volume, $W = \rho_0\psi$. A material with this last property is called *hyperelastic* and the function $W = W(\mathbf{F})$ in this context is sometimes called the *stored-energy function*.

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Constructional Apraxia

Definition

Disability in re-drawing (copying) a drawn figure.

Consummatory Response

Definition

A class of unconditioned responses that occur in response to delivery of a rewarding stimulus (usually food or water). Sucking, chewing, or swallowing might constitute examples of such responses.

►Value-based Learning

Contact Mechanics

Definition

The equilibrium or motion of bodies that are physically touching.

►Measurement Techniques (Pressure)

Content-addressable Memory

►Associative Memory

Context

Definition

Context is the set of static, unchanging cues that define an environment. Cues that are commonly contextual include boundaries, such as wall and semi-distant landmarks (very distant objects, such as celestial objects, are not environment-specific). There are also non-spatial cues that contribute to context, such as permeating odors or persistent sounds. Contexts are important in learning. Contextual learning can be direct association ("in this room I get food rewards") or configural ("if a red light turns on in this room I get food rewards"). Context has been extensively studied in fear conditioning and in the analysis of place cells.

►Hippocampus: Organization, Maturation, and Operation in Cognition and Pathological Conditions
►Spatial Learning/Memory

Context Conditioning

Definition

Cues or stimuli (odors, tastes, sounds or images) from the environment where training occurs that come to be associated with the training, and can be used as cues to trigger memory of the training.

Contextual Amnesia

Definition

►Amnesia

►Source Amnesia

Contextual Fear Conditioning

Definition

Contextual fear-conditioning is a form of Pavlovian conditioning whereby a subject associates a neutral context with an aversive, unconditioned stimulus (US), such as electric footshock. While the shock elicits bouts of jumping and running followed by freezing, the context alone elicits freezing.

►Aversive Learning
►Classical Conditioning (Pavlovian Conditioning)

Contextual Influences in Visual Processing

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Synonyms

Surround influence; Contextual modulation; Local global interaction; Extra-classical receptive field modulation

Definition

Vision is the analysis of patterns in visual images with the view to understanding the objects and the physical processes in the world that generate them. Locally, visual patterns are highly ambiguous and subject to multiple interpretations. Image structures surrounding the pattern being analyzed can provide additional constraints or context to disambiguate the interpretation. The resulting ►contextual influences are ubiquitous in visual perception and manifest at the neuronal level as the modulation of the activity of neurons by image structures outside their ►classical receptive fields.

Characteristics

The study of contextual influences in visual processing has a long history in psychology and neuroscience [1]. Investigations of these effects in the visual system have focused on the ►modulatory effect on the activity of a neuron by image structures outside its localized ►receptive field. The classical approach employs the simplest stimuli such as bars and sinusoidal gratings to probe the interaction between the stimuli presented inside and outside a neuron's classical receptive field. A prevalent finding is that neurons in both the ►primary visual cortex (striate cortex, V1) and the ►extrastriate cortex exhibit ►feature contrast enhancement, i.e., the cells respond better when the stimulus attributes in the area surrounding their receptive fields, such as bar orientation, are different from those inside their receptive fields (Fig. 1a).

Recent approaches seek to understand the neural basis of the perceptual interpretation of the local receptive field stimulus by changing the global image context (Fig. 1b). With this approach, a number of neural correlates of perception have been revealed, providing insights into the representation of subjective perceptual experience in the brain.

Contextual Influences in the Primary Visual Cortex

Neurons in the primary visual cortex receive converging input from the ►lateral geniculate nucleus (LGN). A neuron's classical receptive field, also known as the minimum responsive field, is the part of visual space in which the presence of appropriate features can excite the neuron. By definition, stimulating the visual space outside a neuron's classical receptive field cannot evoke a response. Modulation of neuronal activity by surround stimulation can be observed, however, only when the neuron is responding to a stimulus presented to its receptive field. This modulation is called the non-classical or ►extra-classical receptive field effect. Such effects have been considered neural manifestations of contextual influences in visual perception.

A variety of extra-classical receptive field effects have been identified. A commonly reported phenomenon is called ►surround suppression: the response of a neuron to an oriented bar or grating within its receptive field is suppressed when stimuli are simultaneously introduced to the surrounding area outside its receptive field. There are several types of surround suppression effects, mediated by a number of ►local circuits as well as ►recurrent feedback circuits [2]. The early phase of surround suppression is fast and is not sensitive to the exact parameters of the surround stimuli. However, the later phase of surround suppression is stimulus-specific. Simply put, while the neuron can detect the presence of stimuli in the surround immediately, its sensitivity to the precise nature of the surround stimulus or global context takes time to develop. The onset delay of this

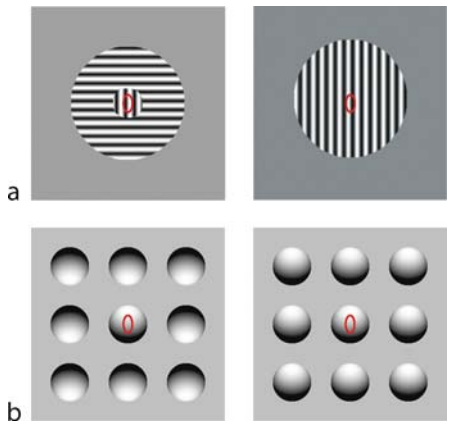
sensitivity varies considerably depending on the types of the stimuli and the spatial extent of the contextual stimuli.

One well-known stimulus-specific surround suppression, observed with an onset delay, is called ►iso-orientation suppression. In this phenomenon, a neuron's response is stronger when the orientation of the surround stimulus is different from that of the center receptive field stimulus than when the orientations are the same. When the receptive field stimulus is a bar, iso-orientation suppression emerges at about 10 ms after the onset of the response to the receptive field stimulus [3]. When the receptive field stimulus is a part of an oriented texture region significantly larger than that of the receptive field, the later part of the neuron's response is inversely proportional to the size of the region – the larger the region, the smaller the response. This results in a relative enhancement of response when the neuron's receptive field is inside a smaller region than when it is in the larger background region. Interestingly, the enhancement is uniform across the surface of a compact region, with a sudden drop off at the region's border. Hence, it has been proposed to be a signal that could highlight a figure against its background and is called the ►figure enhancement effect [4]. According to most studies, the onset delay of this figure enhancement effect is proportional to the size of the region. When the receptive field is at the center of a region that is six times larger than its size, the onset delay is typically 40 ms relative to response onset on the average. The figure enhancement effect is more general than iso-orientation suppression as it has been observed in studies with motion or shape from shading stimuli without any orientation contrast between the receptive field stimulus and the surround [4,5].

Functionally, both iso-orientation suppression and figure enhancement can serve to enhance stimulus feature contrast, resulting in an increase in ►perceptual saliency of the representation of less expected or surprising visual events to facilitate further processing. Indeed, it has been demonstrated that this response enhancement is directly proportional to perceptual saliency of the visual pattern, as measured in terms of the reaction time for target detection, and it is dissociable from luminance contrast or orientation contrast in the stimulus (Fig. 1b) [5]. The broader spatial extent and the longer onset latency of the figure enhancement effect suggest that, while iso-orientation suppression might be mediated primarily by inhibitory ►local circuits, the figure enhancement or perceptual saliency effect likely involves additional long range facilitation circuits including recurrent ►feedback from the extrastriate cortex, as suggested by both anatomical and deactivation studies.

Surround interaction can be quite complex and can vary according to the luminance contrast or the spatial scale of the stimuli. While surround modulation tends to be suppressive when the luminance contrast of the stimulus is strong, it can become facilitatory when the luminance contrast is weak. Neuronal ►adaptation, well known in the ►retina and LGN, is sensitive to the absolute luminance and luminance contrast levels in the entire scene. In a dark and low-contrast environment, retinal and LGN neurons are known to expand their receptive fields temporally and spatially with a simultaneous increase in their sensitivity gains. Such a strategy serves to optimize feature detection in the presence of noise. The contrast dependence of surround influence likely results from V1 neurons inheriting and extending these adaptation or optimization strategies.

Perceptual computations supported by the complex machinery in V1 likely go beyond feature detection and feature contrast enhancement. From a computational perspective, contextual effects reflect the influence of computational constraints, realized by neuronal connectivity and interaction, necessary for solving visual inference problems. Surround interaction can bring in contextual information to improve local estimates



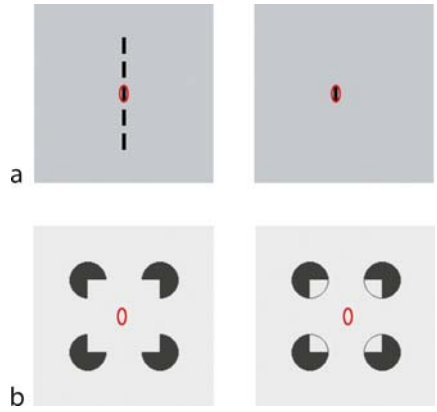
Contextual Influences in Visual Processing.
Figure 1 Stimuli used in contextual modulation studies. (a) Classic center-surround stimuli that have been typically used in neurophysiological studies on iso-orientation surround suppression [3]. Neurons tend to respond better when the orientations of the center and surround gratings are different (*left image*) than when they are the same (*right image*). The red ellipse outlines the spatial extent of the receptive field of the neuron. A similar effect observed in a larger center patch with a significantly longer delay is called figure enhancement [4]. (b) Surround context can change the perceptual saliency of the receptive field stimulus. The receptive field stimulus is said to pop out from the background on the left image, but not on the right image. This pop-out phenomenon depends on 3D interpretation of the stimulus elements. Early visual neurons' activity is correlated with the perceptual saliency of this pop-out phenomenon [5].

of visual cues, as evident in the observations that ►orientation tuning curves and ►disparity tuning curves tend to sharpen over time during the analysis of each visual image. The ►retinotopic organization, the connection infrastructure, and the tuning properties of neurons in V1 make it ideally suitable for supporting a variety of visual computations. One such computation is the grouping of edges into contours and features into coherent regions. There is some evidence that V1 plays an important role in this computation to be discussed below.

First, the activity of some V1 neurons is enhanced if the surrounding bars outside their receptive fields line up with the bar presented within their receptive fields to form a longer contour (Fig. 2a).

Moreover, some V1 neurons respond to the ►subjective contour of a ►Kanizsa figure, even when no feature is presented to their classical receptive fields (Fig. 2b). There is also evidence that neurons can interpolate contours across the blind spot or behind an occlusion. Furthermore, collinear contours have been found to induce neuronal synchrony in V1 neurons of the same ►orientation selectivity. Recently, it was also found that neurons with different orientation tunings, when stimulated simultaneously by curved contours, also exhibit an increase in synchrony or ►effective connectivity, as revealed by multi-electrode recordings [6]. This dynamic change in effective connectivity between neurons as a function of stimulus is suggestive of a mechanism for ►contour completion.

In addition, similar changes in effective connectivity have also been observed among spatially disjoint ►disparity selective neurons when the 3D depth plane of the random dot stereogram stimulus intersects with the cells' optimal disparity tunings. This process appears to contribute to the gradual sharpening of the neurons' disparity tunings over time, providing a plausible mechanism for improving local estimates of visual cues based on global context. Such cooperative or mutual facilitatory mechanisms might also contribute to *surface association* by increasing the firing rates of the neurons analyzing different parts of the same visual surface simultaneously. The resulting enhanced and correlated activities, partly represented in the figure enhancement effect, can highlight the relevant coincident features in visual input as a group to provide a stronger drive for downstream neurons in the extrastriate cortex to learn explicit representations for higher order features and structures.



Contextual Influences in Visual Processing.
Figure 2 Neurophysiological evidence of contour completion in V1. (a) Oriented bars in the surround (*left image*), when aligned with the receptive field stimulus to form a contour, can increase a cell's response to its receptive field stimulus (*right image*) (Kapadia, Westheimer and Gilbert 2000). The *red ellipse* outlines the spatial extent of the receptive field of the neuron. (b) The subjective contour of a Kanizsa's illusory square can evoke response in a V1 neuron even when no stimulus feature is present in its receptive field (*red ellipse*) (Lee and Nguyen 2001). The subtle addition of thin circles on the right image changes the perceptual interpretation of the image from a white square occluding four black circular disks, with a vivid subjective contour over the receptive field (*left image*), to that of a white square in a background visible through four circular windows on a white wall in front (*right image*).

Contextual Influences in the Extrastriate Visual Cortex

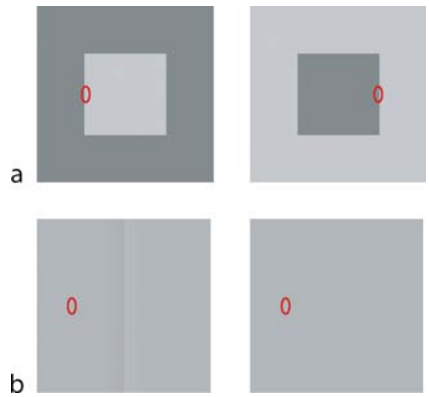
The extrastriate cortex, downstream from the striate or primary visual cortex, is partitioned into many different visual areas. The feature contrast enhancement effect observed in V1 is also prevalent in extrastriate visual areas, expressed in the respective feature dimensions that neurons in those areas are tuned to. In area ►MT (medial temporal), for example, the motion of surround stimuli has been shown to significantly modulate the response of a neuron to moving stimuli presented to its receptive field. The response of the neuron is suppressed when the direction of surround motion is the same as the motion detected in the neuron's receptive field. This is analogous to the iso-orientation suppression in V1 but in the motion domain. In addition, the disparity-tuned MT neurons also experience iso-disparity suppression.

The extrastriate cortical areas, however, exhibit some additional contextual effects that are rarely observed in the striate cortex. Many of these *new* contextual effects are concerned with the inference of 3D surfaces, their occlusion and depth ordering relationships, also known as ►figure-ground organization. In MT, it has been shown that the responses of direction-selective neurons to a motion stimulus are sensitive to the figure-ground context defined by the surrounding surface depth structures in a way that is consistent with ►Barber Pole illusion [7].

Several lines of evidence suggest that the computations underlying figure-ground segregation and 3D surface inference might start in visual area V2. First, a significant fraction of V2 neurons (and a small number of V1 neurons) have been shown to signal whether their receptive fields are at the left border or the right border of a figure in an image regardless of the polarity of contrast at the border (Fig. 3a).

A left-border-preferring neuron carries the information that the border within its receptive field belongs to (or is *owned* by) the surface or region to its right [8]. A complementary, right-border-preferring neuron exists at the same location, and both neurons could form a push–pull pair for every border orientation. The activity of a set of such pairs of ►border-ownership neurons in various orientations along the border of each region in an image can encode the depth-order relationship between the different image regions or inferred surfaces. Secondly, it has been found that neurons in V2, but not in V1, are sensitive to the mismatch in features between the images from each eye at visual locations where one surface occludes another [9]. The emergence of sensitivity to this surface occlusion cue in V2, known as the ►Da Vinci stereo, further suggests that 3D surfaces and their occlusions are explicitly represented in V2. The figure-ground context made explicit in V2 could feed back to constrain the computation in V1, resulting in, for example, the figure enhancement effect. However, it should be noted that the figure enhancement effect in V1 has not been conclusively demonstrated to depend solely on figure-ground organization.

The perception of surface attributes such as brightness, shading and color depends very strongly on the interpretation of the underlying 3D surface geometry and the illumination direction in the visual scene. Two observations suggest that these surface attributes might also be inferred and represented in V2 because of the dependence of such inference on 3D surface interpretation. First, the neural correlate of ►shape-from-shading pop-out, a perceptual phenomenon that crucially depends on 3D surface interpretation, is observed in V2 but not in V1 pre-attentively [4]. Second, the neural correlate of the ►Cornsweet-O'Brien illusion, an illusion in perceived brightness induced by edge contrast, which ultimately can be traced back to surface geometry and lighting direction interpretations in natural scenes, is observed in V2 but not V1 [10] (Fig. 3b). There has been, however, some evidence for brightness representation in V1 [1]. It is possible that the construction of brightness representation is a gradual and distributed process, computed first at V1 based on surround luminance contrast, but achieving a more abstract and invariant representation in V2 as the 3D surface representation is made explicit. In general, neuronal activities tend to become progressively more abstract and more correlated with our subjective perceptual experience as one moves up the visual hierarchy.



Contextual Influences in Visual Processing.
Figure 3 Neurophysiological evidence of surface inference in V2. (a) A left-border cell will respond more strongly when its receptive field (*red ellipse*) is analyzing the left border of a figure (*left image*) than when it is analyzing the right border of the figure (*right image*), even when the visual pattern on the receptive field and in its immediate surround is identical [8]. This class of cells, observed primarily in V2, is said to convey information about border-ownership or surface occlusion. (b) In the Cornsweet-O'Brien illusion, the presence of a contrast edge can change the perception of the brightness of a region. A V2 neuron that prefers darkness over brightness would respond better to the perceptually darker region (*left image*) than to the perceptually brighter region (*right image*) even though the physical luminance of the receptive field stimulus in the two cases is exactly the same [10].

In addition to global image structures, behavior, task demands and memory are also known to provide strong contextual information to influence visual perception and object recognition. ►Attentional modulation of neuronal responses has been widely observed and studied in the extrastriate cortex (see ►Visual Attention). Attentional effects in V1 are subtle and observable mostly when visual scenes are cluttered or in tasks that demand considerable spatial attention at precise locations such as the task of tracing a curve. Beyond V2, extrastriate neurons tend to have large receptive fields. Attentional modulation in neurons of these higher areas typically manifests as the selection of one relevant feature over the others present within their individual receptive fields. Attention can be voluntary, as in selecting a particular spatial location (spatial attention) or a particular feature (feature attention) in the receptive field for further analysis. But it can also be reflexive, driven or captured by the saliency of the stimuli computed automatically in early visual areas. The variety of ►feature contrast and perceptual saliency effects observed in V1 and in the extrastriate cortex likely serve as a part of this reflexive attention mechanism. Recently, higher-order non-spatial

contextual effects, such as context familiarity and associative memory, have also been shown to modify the activities of neurons in ►inferotemporal cortex (IT) and medial temporal (MT) respectively.

From the perspective that vision is a process for inferring the various underlying environmental causes of visual patterns such as the 3D geometry of surfaces, the identities of objects and the illumination direction in the scene, the extrastriate areas in the visual hierarchical system might be conceptualized as modules that provide explicit representation of these decomposable causes. Each extrastriate module furnishes an explanation on some aspect of the visual scene. The inference of the underlying causes involves integration of information across space and over time by neurons in the higher-order visual areas, which in turn provide a variety of context in which visual processing in the earlier visual areas can be refined. V1, with its neurons arranged in a spatially precise ►retinotopic map and endowed with small localized receptive fields capable of representing fine details in images, might serve as a *high resolution buffer* at which all the causes are combined together to synthesize an explanation of the visual input represented explicitly there. These interactive computations can bring about a very rich set of contextual influences in V1 and the extrastriate cortex. The long latency of many of the contextual effects observed suggests that a substantial amount of recurrent interaction could have taken place. Computations involving such recurrent interaction predict the *simultaneous* emergence of the perception-related signals in many visual and decision areas in the brain.

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Contextual Modulation

►Contextual Influences in Visual Processing

Contextualist Theories of Knowledge

Definition

Contextualist theories of knowledge (at least those in the narrow sense of the term) claim that, in order to answer the question whether or not S knows that p, the context of the person ascribing knowledge has to be taken into account. The consequence is that, according to these theories, there is no ascriber independent "fact of the matter" about knowledge.

►Knowledge

Contig

Definition

DNA sequence that is assembled from overlapping shorter sequences to form one large contigous sequence.

Continuity Equation

Definition

A traditional name for the law of conservation of mass.

►Mechanics

Continuous Growth and Remodeling

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Definition

A process of growth consists of the addition or removal of mass from a ►material body. In a continuum framework, volumetric (or bulk) growth and surface growth can be distinguished. The term remodeling is applied to instances in which there is a reorganization of material particles without any net growth.

Description of the Theory

The theories of continuous growth and remodeling, as well as more general theories of morphogenesis, are still in a stage of development and have not yet attained a definitive standard form. For this reason, this paper will be limited to the presentation of some fundamental theoretical notions based on a particular point of view (in line with ►continuum mechanics) and confined to certain types of phenomena. According to this point of view, growth and remodeling are particular instances of phenomena of ►*material evolution* in which the identities of the material particles, as well as their constitutive nature, are preserved. What changes, then, is the way they are mutually arranged in the body. These changes are not to be confused with the motion in space: they refer to a different type of "motion" taking place in the body itself. If material snapshots were possible, the body at different instants of time would still be seen as made of the same material, but would be busy accommodating the material neighborhoods relative to each other. Each snapshot might reveal the presence of continuous distributions of dislocations and it is this presence that can be seen as responsible for the development of, among other effects, residual ►stresses associated with the processes of growth and remodeling.

As a point of departure for a more general treatment, consider first a material body each of whose points abides by a purely elastic response. To make matters even simpler, assume that the body is *hyperelastic* as defined in the constitutive theory (q.v.), the mechanical response at each material point is completely characterized by a single scalar function W measuring the stored elastic energy per unit volume of a reference ►configuration. The independent variables of this function are the ►deformation gradient $\mathbf{F}$ and the body point $\mathbf{X}$. The derivative of W with respect to $\mathbf{F}$ at a point $\mathbf{X}$ is equal to the ►first Piola-Kirchhoff stress tensor $\mathbf{T}$ at that point. The first question that comes to mind is the following: given a function $W = W(\mathbf{F}, \mathbf{X})$, namely, a hyperelastic material response with respect to some reference configuration, can it be unequivocally ascertained that all the points of the body are made of the same material? At first sight, the answer to this question seems to be that this will be the case if the response function W happens to be independent of the point $\mathbf{X}$. A moment's reflection, however, reveals that, although this condition is certainly sufficient, it is by no means necessary for a positive answer. To understand why this is the case, assume that there is indeed a reference configuration for which the response function W is independent of $\mathbf{X}$. If the reference configuration (as per Eq. 9 in ►kinematics of deformation (q.v.)), is now changed there would be a new expression for the stored-energy function W' per unit volume of the new reference configuration:

$$W'(\mathbf{F}, \mathbf{Y}) = J_H^{-1}\, W(\mathbf{F}\mathbf{H}(\mathbf{X})). \tag{1}$$

In this equation, the change of reference configuration is represented (as in Eq. 9 of kinematics of deformation) by a function $\mathbf{Y} = \mathbf{Y}(\mathbf{X})$, whose gradient is denoted by $\mathbf{H}$. The determinant J_H of $\mathbf{H}$ appears in the equation because W' is evaluated per unit volume of the new reference configuration. The main point is that in the new reference configuration there is an *explicit dependence on the body point* $\mathbf{Y}$, even though the body is exactly the same as before! What this means is that a ►constitutive law may appear to indicate a dependence on the body point, but this may be due only to an unhappy choice of reference configuration. In some cases no happy choice exists and yet the material may be the same at all points of the body.

Inspired by Eq. 1, the concept of ►*material isomorphism* can be introduced. Two points, $\mathbf{X}_1$ and $\mathbf{X}_2$, of a body with constitutive law $W = W(\mathbf{F}, \mathbf{X})$ are said to be *materially isomorphic*, if there exists a non-singular two point tensor $\mathbf{P}_{12}$ such that the equation:

$$W(\mathbf{F}, \mathbf{X}_2) = J_{P_{12}}^{-1}\, W(\mathbf{F}\mathbf{P}_{12}, \mathbf{X}_1) \tag{2}$$

is satisfied *identically* for all deformation gradients $\mathbf{F}$. From the physical point of view this formula has a very simple explanation: If a small neighborhood has been surgically cut around point $\mathbf{X}_1$, given a deformation $\mathbf{P}_{12}$ and then implanted in place of a neighborhood of point $\mathbf{X}_2$ and if, after performing this *transplant operation* it is impossible to detect by any mechanical experiment that the operation has taken place, then the material must have been the same at both points to begin with. Otherwise, such a perfect graft would not have been possible. A body is said to be *materially uniform* if all of its points are mutually materially isomorphic. In other words, material ►uniformity corresponds exactly to the positive answer to the question of departure. A function W that passes the test of material uniformity corresponds to a body that is made of the same (hyperelastic)

material at all points. Clearly, material isomorphism is an equivalence relation: (i) every point is materially isomorphic to itself (choosing $\mathbf{P}_{11} = \mathbf{I}$); (ii) if $\mathbf{X}_1$ is materially isomorphic to $\mathbf{X}_2$, then $\mathbf{X}_2$ is materially isomorphic to $\mathbf{X}_1$ (choosing $\mathbf{P}_{21} = \mathbf{P}_{12}^{-1}$); (iii) if $\mathbf{X}_1$ is materially isomorphic to $\mathbf{X}_2$, and $\mathbf{X}_2$ is materially isomorphic to $\mathbf{X}_3$, then $\mathbf{X}_1$ is materially isomorphic to $\mathbf{X}_3$ (choosing $\mathbf{P}_{13} = \mathbf{P}_{23}\,\mathbf{P}_{12}$). In other words, a materially uniform body can also be defined as one for which all of its points are materially isomorphic to a fixed reference point $\mathbf{X}_0$. Imagine that this reference point has been placed outside of the body as some kind of *archetype* or pattern that describes the generic behavior of all points of the body. Introducing the notation $\mathbf{P}(\mathbf{X}) = \mathbf{P}_{0X}$ for the transplant operations from the archetype to an arbitrary point $\mathbf{X}$ and denoting the archetypal stored energy function by $\overline{W}$, Eq. 2 may be rewritten as:

$$W(\mathbf{F}, \mathbf{X}) = J_P^{-1}\, \overline{W}(\mathbf{F}\mathbf{P}(\mathbf{X})). \tag{3}$$

Thus, a body is uniform if there exists a *field of implants* $\mathbf{P}(\mathbf{X})$ such that Eq. 3 is satisfied identically for all deformation gradients $\mathbf{F}$. This equation clearly shows that a dependence on material point in itself is not an indication of lack of material uniformity, as long as this dependence is restricted by the multiplicative composition indicated in Eq. 3.

A material point may be non-trivially materially isomorphic to itself. That is, there may exist material automorphisms $\mathbf{G}_X = \mathbf{P}_{XX} \neq \mathbf{I}$. Such tensors are called *material symmetries* of the point in question. For physical reasons, they are always assumed to have a unit determinant, since it is expected that the material response will always be affected by a change of volume. It is not difficult to verify that all material symmetries of a point form a group under the operation of matrix composition. This group, called the *symmetry group* of the point, is a subgroup of the *unimodular group*, namely, the group of matrices with unit determinant. An elastic material point is called an *elastic solid* if there exists a reference configuration for which the symmetry group is a subgroup of the orthogonal group. Such a configuration is called a *natural state*. If the symmetry group coincides with the orthogonal group, the solid is fully *isotropic* (its response is indifferent to any pre-imposed rotation). Clearly, if $\mathbf{G}_1$ is a ▶material symmetry of point $\mathbf{X}_1$ and if $\mathbf{P}_{12}$ is a material isomorphism between $\mathbf{X}_1$ and $\mathbf{X}_2$, then the composition $\mathbf{P}_{12}\mathbf{G}_1$ is also such a material isomorphism. In other words, the material isomorphisms between points of a uniform body are not unique if the points have a non-trivial symmetry group. As expected, the symmetry groups at different points of a uniform body are not independent of each other. Indeed, it is not difficult to verify that, with the same notation as above, the map $\mathbf{G}_2 = \mathbf{P}_{12}\,\mathbf{G}_1\,\mathbf{P}_{12}^{-1}$ is a symmetry at point $\mathbf{X}_2$ and that all symmetries at this point can be obtained in this way. Technically, the symmetry groups at all points are *conjugate* of each other and therefore, also conjugate to the symmetry group of the archetype.

Given a materially uniform body it may so happen that, in some reference configuration, there exists a trivial field of implants, namely, a field consisting just of a translation of the archetype to each point; the grafts are achieved without any distortion or rotation. If this is the case, the uniform body is said to be *globally homogeneous* and the special reference configuration is a *homogeneous configuration*. Without entering into the technical details, there exist uniform bodies that are not globally homogeneous (for example, a homogeneous bar that has been closed by perfectly welding its ends in a ring-like fashion, is not globally homogeneous; notice that in this example the lack of ▶homogeneity manifests itself in the impossibility of releasing the stresses simultaneously at all points of the ring). One may think that a uniform body may always be considered as *locally homogeneous*, that is, homogeneous by pieces (the example of the ring seems to suggest so, since any piece of the ring can always be rectified, if not the complete ring). Unfortunately, this is not the case, and it is not difficult to construct examples of locally inhomogeneous uniform bodies. Physically, they correspond, for example, to bodies with continuous distributions of dislocations.

So as to link these ideas to the biological problems of growth and remodeling, imagine that the implants $\mathbf{P}(\mathbf{X})$ are allowed to evolve in time, namely to become functions $\mathbf{P}(\mathbf{X}, t)$. This process is called a *material evolution*. It is critical to realize that, even though the material archetype remains always hyperelastic, the admission of a material evolution into the physical picture results in a non-elastic response of the different points of the body. The simplest image of what is going on is obtained by thinking of the body as an array of ▶linear springs, all having the same stiffness constant. The implant operation $\mathbf{P}(\mathbf{X})$ boils down in this case to a stretch of the archetypal spring before inserting it in each position within the body. A material evolution can then be interpreted as a change of resting length of the inserted spring as time goes on. This example should not be pushed too far, but it is certainly a good heuristic picture to keep in mind. If the material evolution takes place at a given point in such a way that the determinant of the implant keeps a constant value, it is said that *remodeling* is taking place. If, on the other hand, the determinant changes in time, a process of *volumetric growth or resorption* is also at play, since it is easy to verify that in this case the mass *is not conserved*. From the purely formal point of view, therefore, the various theories of growth and remodeling are similar to the theory of plasticity with finite ▶strains. As evolution takes place, it is clear that even if the material body is

initially homogeneous it will in general cease to be so and internal stresses will in general appear due to the material rearrangement processes taking place. It is also possible for biological systems in particular to have a natural tendency to produce a material evolution that tends to eliminate these residual stresses in the long run.

To complete a theory of growth or remodeling, in addition to important modifications to be introduced into the conventional ▶balance laws (q.v.), it is necessary to specify some *constitutive law of evolution* dictating, for example, how the first ▶time-derivative of the implants is related to the stresses in the material. Although the details of the underlying constitutive theory are beyond the scope of this article, it is interesting to notice that if the stored-energy function is identified with the ▶free energy (of Helmholtz) per unit volume, then it turns out that, in the same way as the derivative of Eq. 3 with respect to **F** yields the first Piola-Kirchhoff stress, the derivative of the same equation with respect to the implant field **P**(**X**) yields another measure of stress called the ▶*Eshelby stress*. More specifically:

$$\frac{\partial W}{\partial \mathbf{P}} = \mathbf{P}^{-1}(-W\,\mathbf{I} + \mathbf{F}^T\,\mathbf{T}) \tag{4}$$

where the formula for the derivative of a determinant has been used. The quantity within parentheses, namely $\mathbf{b} = -W\,\mathbf{I} + \mathbf{F}^T\,\mathbf{T}$, which can be expressed in component form as:

$$b^I_J = -W\,\delta^I_J + F^i{}_J\,T^I_i, \tag{5}$$

is the Eshelby stress tensor. It is a purely referential tensor. From its derivation, it is clear that the Eshelby stress is a measure of the free energy per unit volume consumed in producing a material change in the body (such as growth or remodeling) and it is legitimate to identify it with some kind of *material or configurational force* in contradistinction with the spatial or Newtonian forces of conventional mechanics (▶Newtonian Mechanics). Configurational forces of various kinds are the subject of intense research in present-day continuum mechanics.

The Eshelby stress is thus the thermodynamic dual of the material implant **P**. A possible law of evolution may, therefore, have the form:

$$\dot{\mathbf{P}} = f(\mathbf{b}, \mathbf{P}), \tag{6}$$

where f is some tensor-valued function depending of the material and the phenomenon being modeled. By requiring that the form of the law be independent of the reference configuration used, this law can be reduced to the form:

$$\overline{\mathbf{L}}_P = f(\overline{\mathbf{b}}), \tag{7}$$

where

$$\overline{\mathbf{L}}_P = \mathbf{P}^{-1}\dot{\mathbf{P}} \tag{8}$$

is a measure of the velocity of remodeling, somewhat like a material counterpart of the spatial ▶velocity gradient (although $\overline{\mathbf{L}}_P$ is not a gradient in general). The overbar is meant to remind that this quantity is an automorphism of the archetype. Similarly, the argument $\overline{\mathbf{b}}$ represents the Eshelby stress pulled back to the archetype, namely:

$$\overline{\mathbf{b}} = J_P\,\mathbf{P}^T\mathbf{b}\,\mathbf{P}^{-T}. \tag{9}$$

Thus, the evolution law, Eq. 7, depends only on the archetype chosen, as it should. There is still another restriction to the evolution law, which stems from the symmetry group of the material. This is called the *principle of actual evolution*. Recall that if **P** is a material isomorphism between the archetype and some point in the body, so is the product **PG**, where **G** is an arbitrary member of the symmetry group of the archetype. Thus, there is a certain degree of freedom in the choice of implant. If the symmetry group is continuous, therefore, it is possible that the form of the function f be such that the instantaneous change of implant prescribed by Eq. 7 may fall within this degree of freedom. In such a case, the evolution would be fictitious and would not represent a true material rearrangement. To avoid such a situation, the function f must provide a result, which is never equal to a "small" element of the symmetry group of the archetype. In other words, this function must always give a result that falls outside the Lie algebra of the symmetry group. As an example, consider the case of a fully isotropic solid. Assuming that the archetype is in a natural state, the symmetry group of the archetype is the orthogonal group. The Lie algebra consists of all skew-symmetric matrices (infinitesimal rotations). The tensor function f, therefore, must not be skew-symmetric. Put in a different way, the law of evolution must specify a non-vanishing evolution for the symmetric part of $\overline{\mathbf{L}}_P$. On the other hand, if the material is not fully isotropic (for example, if its symmetry group is discrete), then even a skew-symmetric function f represents a legitimate evolution.

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Continuum Mechanics

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Definition

Continuum ►mechanics studies the motion of material bodies taking into consideration their deformability. It does not make any a-priori distinction between different states of matter (solid, liquid, gaseous), but it does generally assume that the underlying medium is continuous. Technically speaking, the medium is assumed to be a ►differentiable manifold, so that smoothly varying *fields* can be defined on it (►velocity, ►stress, temperature and so on). A more appropriate name for the discipline might have been continuum thermomechanics, since thermodynamical effects are an essential part of its scope.

Description of the Theory

Although the historical origins of continuum mechanics can be traced back to, among others, Euler and Cauchy and although by the first half of the twentieth century a variety of particular theories (►elasticity, fluid mechanics, plasticity, etcetera) had been successfully applied to many areas of engineering, it is commonly agreed that the term continuum mechanics refers to the rigorous unified treatment undertaken starting from the 1950's and still very much underway in today. The by now standard treatment of the subject can be neatly divided into three parts, ►kinematics of deformation ►balance laws and constitutive theory. While the first two parts enunciate general definitions and principles applicable to all bodies, the third part deals with the description of particular classes of ideal materials, whose behavior may be used to approximate the response of real materials, at least under certain restricted conditions (for example, relatively small ►strains, isothermal processes and so on). Nevertheless, whereas the range of applicability of an ideal material model to a particular real material may be so restricted, one of the tenets of continuum mechanics is that, once the parameters of an ideal model have been established, no further limitations are to be imposed. To be more precise, ideal material models are formulated in terms of constitutive equations, which express the generic functional dependence of certain physical quantities (stress, heat flux, ►internal energy, etc) in terms of other quantities (motion, temperature, etc). An ideal material is completely characterized by the choice of these variables (for example, the present value of the temperature, rather than its whole past history may be considered), but their range is not limited a priori. For biomechanics in particular, the possibility of not avoiding (as would have been the case in the older treatments) the exploration of a wide range of deformability is of paramount importance and it can be said that biological systems constitute a natural source of material models that is and will continue to be behind much of the cutting edge activity in continuum mechanics. Apart from the more conventional theories, biological systems necessitate the application of ►mixture theory (with and without chemically reacting components), smart materials (activated by external agents) and theories of continuous ►growth and remodeling (involving laws of evolution driven by so-called ►configurational forces).

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Contours

Definition

►Form Perception

Contractile Element

Definition

In muscle mechanics. A rheological element that can slide freely with no force unless it is "activated," in which case the force is given by an ad hoc (experimentally based) law.

►Mechanics

Contraction-induced Injury

Definition

An experimental method of causing injury to an isolated skeletal muscle, typically dissected from a mouse or rat, to determine under what conditions the components of the muscle fibers will become injured when they are contracting while being stretched. It is a method suitable for comparing dystrophic versus non-dystrophic skeletal muscle integrity.

Contralateral Visual Field

Definition

The region of visual space that extends from the vertical meridian (which passes through the center of gaze) peripherally toward the side of the body opposite to the neuron or brain region studied. In general, each side of the brain processes information from the contralateral visual field.

►Visual Field

Contrast

Definition

In sensory systems, contrast is a measure of relative stimulus intensity at some point in relation to the average (background) intensity level.

►Sensory Systems

Contrast Enhancement

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Synonyms

Receptive field selectivity; Edge enhancement; Sharpening; Acutance; Unsharp masking; Selective feature enhancement; Decorrelation

Definition

Contrast enhancement is a transformation of a sensory representation that results in an output representation in which regions of transition (e.g. "edges") are selectively emphasized. The mechanisms mediating contrast enhancement in different systems are diverse, depending critically on the breadth of the contrast enhancement function as well as on the modality of the representation.

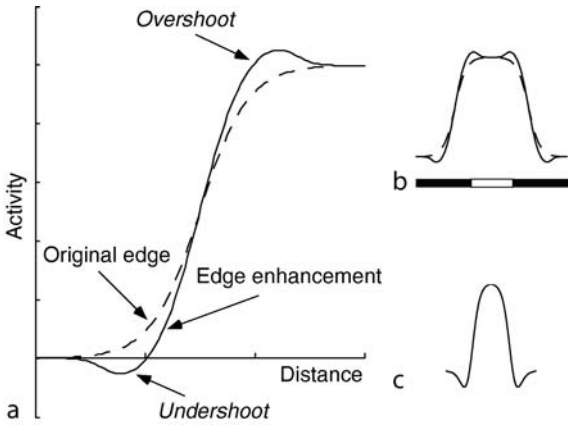
Characteristics

Quantitative Description Across Modalities and Scales

The utility of contrast enhancement is broadly familiar from photography, particularly digital photography, in which it is employed to help compensate for the physical limitations of photographic equipment in comparison to the capacities of the human visual system. Indeed, several image processing techniques including contrast enhancement resemble stimulus-transformation processes embedded in animal sensory systems. Interestingly, the essential function of contrast enhancement is remarkably similar among sensory modalities (e.g. vision, audition, olfaction) as well as between these biological systems and photographic image processing, although the algorithms and neural mechanisms mediating this transformation differ substantially according to the differing constraints of these systems.

Contrast enhancement is a general term encompassing a range of related operations distinguished by *scale* (or *breadth*), which in this context refers to the maximum distance from any given point in an image or sensory representation at which local activity exerts an influence over the contrast enhancement operation. The simplest, smallest-scale contrast enhancement operation is edge enhancement (Figs. 1a–c).

Neighboring points in a sensory representation (or photographic image) that differ in intensity (e.g. brightness) are transformed so that these differences are accentuated. Specifically, local changes in intensity are emphasized by increasing *acutance*, the local derivative of intensity with respect to space. In digital photography, the most common algorithm for edge enhancement is the



Contrast Enhancement. Figure 1 Contrast enhancement functions. In all figures, the abscissa represents distance in the appropriate metric space (e.g. spatial location for visual retinotopy, frequency for audition, or odor similarity for olfaction), whereas the ordinate represents activity. (a) Edge enhancement. The original edge of the image or representation (dashed line) smoothly transitions from a low-activity (e.g. dark) region to a high-activity (e.g. bright) region. After edge enhancement (solid line), the acutance (maximum slope of the curve) has been increased. Additionally, both unsharp masking and lateral inhibition can produce regions of overshoot adjacent to the edge, which further emphasize the transition. This is the basis for the perception of Mach bands. (b) The "Mexican hat" function representing on-center/inhibitory surround contrast enhancement, here depicted in one dimension. Dashed line: activity profile induced by a stimulus (white bar) on a blank background (dark bar). Solid line: activity profile after edge enhancement. (c) Another form of the Mexican hat function in which the activated region is smaller than the scale of the contrast enhancement function and hence can be approximated by a point. Consequently, this form of the function does not exhibit prominent overshoots, though it does exhibit undershoots (surround inhibition).

►unsharp mask, whereas in the retina of the eye (for example) this transformation is instead mediated by lateral inhibitory synaptic interactions among neighboring neurons. Because both these operations utilize only information from immediately adjacent locations within the representation, they are considered to operate on the smallest relevant scale. At the other extreme of scale, in which the unsharp mask is uniform or, equivalently, lateral inhibitory interactions are uniform in strength and connect all possible pairs of neurons irrespective of distance, the resulting transformation is a global normalization roughly comparable to a *z*-score [1]. Winner-take-all and winner-take-most algorithms are potential variants of this global-scale contrast enhancement operation.

Contrast enhancement operations acting at intermediate scales are of considerable computational interest in neural systems. Potentially, they can address the global dynamic range problem created by sensory scenes in which different regions of potential interest exhibit substantially different mean intensities. Normally, in sensory scenes with distinct regions exhibiting widely different mean intensities, a simple optimization of the sensory system for the properties of one selected region renders it correspondingly poorly optimized for dissimilar regions. For example, setting a camera to capture the detail of a well-lit surface can result in the detail of darker regions within that photograph being lost. In digital image processing, local contrast enhancement, which operates on a scale between edge enhancement and global normalization, alleviates this problem by transforming images with respect to the intensity of a somewhat broader region surrounding each point. The underlying algorithm is typically a simple unsharp masking on a larger scale (i.e. greater blur distance) than is used for edge enhancement; however, superior results can be obtained by utilizing more complex, scene-dependent adaptive transfer functions integrating multiple independent samples. The analogous operations in biological sensory systems are topics of substantial interest and debate.

In each of these examples, an ordered topology among sensors is a necessary prerequisite for contrast enhancement computations. That is, the array of sensors must be somehow organized so that computations can be selectively performed among sensors with respect to the similarity (or degree of overlap) of their receptive fields. The degree of receptive field dissimilarity is referred to as *distance* – not necessarily based on physical space but rather on a distance ►metric based on this ordered topology of stimulus similarity. For example, in digital image processing, creating an unsharp mask requires specification of the blur distance, which in turn requires a metric with which to compute distance and proximity in visual space. In the retina, physically neighboring visual neurons mediate correspondingly similar spatial receptive fields; hence, physical proximity naturally reflects receptive field similarity. In the auditory modality, the analogous similarity metric is frequency. While frequency is not an intrinsically spatial stimulus feature, the ordered distribution of frequency selectivity along the cochlea again enables the physical proximity of higher-order sensory neurons to reflect the similarity of their receptive fields. That is, these two neural systems are organized specifically so as to be able to utilize physical proximity to represent receptive field similarity, which renders effective the use of neural algorithms dependent on physical proximity, such as nearest-neighbor lateral inhibition. This solution is not effective in all modalities, however, as is discussed below.

Contrast enhancement is in essence a nonuniform rescaling of intensity information across a sensory scene that accentuates certain features of the sensory

scene in exchange for a theoretical loss of absolute intensity information among those features. (This may result in little practical loss when the absolute range of intensities exceeds the instantaneous dynamic range of the sensory system). The scale of the contrast enhancement operation determines its function, which can range from edge enhancement at the smallest scales to global intensity normalization (e.g. exposure control) at the largest scale, with substantial potential at intermediate scales to contribute to selective feature extraction. While these definitions and principles are generally applicable, effective neural mechanisms for computing contrast enhancement operations depend critically on the properties and constraints of each sensory modality.

Olfactory Contrast Enhancement

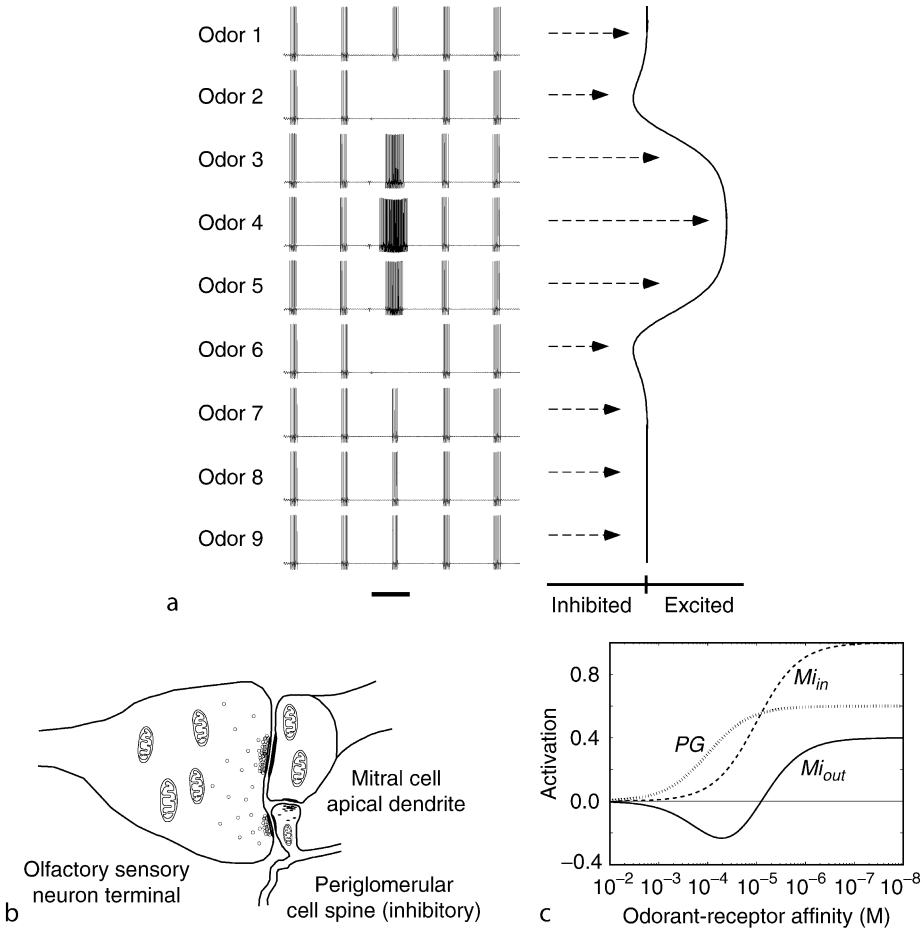
Contrast enhancement operations are clearly evident within the olfactory system. Specifically, they are directly observable in the activity profiles of second-order principal sensory neurons, known as mitral cells, located within the olfactory bulb [2] (Fig. 2a).

Odor stimuli evoke characteristic activity profiles across a broad range of different primary olfactory sensory neurons (OSNs); some OSNs become strongly activated by a given odorant while others are activated weakly or not at all. OSNs synapse directly onto mitral cell dendrites, as well as onto periglomerular cell spines which subsequently inhibit the same mitral cell dendrites (Fig. 2b). Consequently, mitral cell responses to odorants can be either predominantly excitatory or inhibitory, and have been shown to exhibit "Mexican hat" tuning curves for odor stimuli; i.e. odorants that are structurally and perceptually similar to those evoking peak activity in a given mitral cell evoke the strongest inhibitory responses from that cell (Figs. 1c and 2a). In other words, mitral cell response profiles exhibit "on-center, inhibitory surround" receptive fields, in which the metric that defines this "surround" is based on chemical similarity rather than on physical space. This unique similarity metric necessitates an underlying neural mechanism quite different from those utilized by the visual and auditory systems.

Principles of Operation

Olfactory contrast enhancement and its underlying neural mechanisms exhibit important differences from their visual and auditory counterparts. First, of course, the similarity metric in olfaction is unique. In visual *retinotopy*, neuronal receptive fields naturally overlap in proportion to their spatial proximity; in audition, the cochleotopic mapping of auditory frequency selectivity accomplishes the same effect, enabling spatial proximity to be utilized as a proxy for receptive field similarity in subsequent neural computations. Consequently, nearest-neighbor lateral inhibitory synaptic interactions are able to mediate small-scale contrast enhancement in both these systems, though in audition the similarity metric is defined along the single dimension of frequency rather than the two-dimensional matrix of retinotopic space. The similarity metric in olfaction is somewhat more complex. Primary olfactory receptivity is mediated by ligand-receptor interactions between odorant molecules and a population of hundreds of different cell surface receptors expressed (in vertebrates) in ciliary membranes lining the olfactory epithelium within the nasal cavity. The different classes of olfactory receptor each respond to a range of structurally related molecular epitopes (*odotopes*; [4]), and the chemical receptive fields of different receptor classes overlap substantially, such that even single-molecule odorant stimuli can evoke activity in a substantial number of differently-tuned sensory neurons. Because of these broad receptive fields, structurally similar odorant molecules evoke correspondingly overlapping patterns of activity in the olfactory bulb and their odors are perceived as correspondingly similar in quality [5]. However, because of the number of receptor classes, the similarity metric is also high-dimensional (in principle, the number of dimensions should correspond to the number of different odorant receptors expressed; [4]). Consequently, a distance matrix of odorant similarities, whether defined perceptually or in terms of neuronal activation profiles, cannot be continuously mapped onto a one- or two-dimensional surface as can the cochleotopic or retinotopic maps of the auditory and visual modalities. Rather, such ►metric spaces must be mapped discontinuously when mapped onto lower-dimensional spaces such as the two-dimensional cortical layer of the olfactory bulb, thereby exhibiting exactly the sort of fragmented topology exhibited in the glomerular layer of the olfactory bulb. Nearest-neighbor lateral inhibition is therefore ruled out as a possible underlying neural mechanism for olfactory contrast enhancement.

Olfactory contrast enhancement entails sharpening mitral cell receptive fields so that the population activated by a given odorant is more specific and the overlap between the representations of similar odorants is correspondingly reduced. That is, an operation must be performed that is analogous to lateral inhibition, but that is effective in a high-dimensional metric space. A non-topographical mechanism for olfactory contrast enhancement has been proposed that is independent of the proximity among activated neurons, combining a small-scale contrast enhancement mechanism with a qualitatively distinct global-scale mechanism mediating feedback normalization among activated mitral cells [1,3]. While the mechanisms are unrelated, the resulting transformation is comparable to that which would be mediated by a "lateral" inhibitory mechanism mapped directly onto the high-dimensional topology of similarity among OSN receptive fields.



Contrast Enhancement. Figure 2 Features of olfactory contrast enhancement. (a) Computational model of non-topographical contrast enhancement [3] replicating the canonical demonstration of olfactory contrast enhancement among olfactory bulb mitral cells [2]. Activity from a single mitral cell is illustrated over five inhalation cycles; the cell exhibits weak periodic background activity in response to inhalation of room air. One 2-second odor stimulus is delivered during the third inhalation cycle (denoted by black bar). Nine different odors are presented that vary sequentially in structural and perceptual similarity (odors 1–9, corresponding to a homologous series of *n*-aliphatic aldehydes in [2]). Here, odor 4 is near the center of this cell's receptive field, with its neighboring odorants also evoking activity and odors 2 and 6 evoking a net inhibition. This response profile reflects a Mexican hat contrast enhancement function, as illustrated to the right, based on a metric of odor similarity. (b) Illustration of the synaptic triad between OSN axonal terminals, mitral cell apical dendrites, and the spines of inhibitory periglomerular interneurons. OSN activity is communicated to the mitral cell both directly as excitation and via the periglomerular cell as inhibition. (c) Illustration of the central principle of non-topographical contrast enhancement [3]. The higher input resistance and smaller volume of periglomerular spines (PG) is proposed to generate a more sensitive voltage response to similar OSN inputs compared with mitral cell dendrites (Mi_{in}), but also to saturate at a level that the latter can overcome. The result is a nonmonotonic "half-hat" response profile of mitral cells to odorants of varying quality ($Mi_{out} = Mi_{in} - PG$), in which high-affinity odorants evoke excitation, medium-affinity odorants evoke inhibition, and low-affinity odorants evoke no response from mitral cells, yielding odor response profiles as shown in a. Further details in [1,3,4].

Regulation of Olfactory Contrast Enhancement

Many factors – behavioral, situational, pharmacological, and genetic – affect the perceptual differentiation among similar odorants that is influenced by contrast enhancement. The clearest correspondence to date between such perceptual differentiation and the regulation of contrast enhancement at the neural circuit level, however, is the neuromodulation of olfactory bulb circuitry by acetylcholine. Nicotinic cholinergic agonists excite both mitral and periglomerular neurons in the olfactory bulb [6], yielding a concerted response predicted by the non-topographical contrast enhancement model to sharpen mitral cell tuning curves. Indeed, infusion of cholinergic agonists into

the olfactory bulb evokes sharper behavioral differentiation among odorants [7]. The implication of this example is that olfactory contrast enhancement is plastic, with differentiation among odor representations dynamically regulated in accordance with variables such as learning, motivation and behavioral state.

Contrast Enhancement and Olfactory Function

The function of contrast enhancement in any system is to differentially emphasize particular features within a sensory scene. Traditionally, this process of feature selection is discussed with reference to the physical attributes of sensory scenes: e.g. visual edges, or the relative differentiation among structurally similar odorant stimuli; however, this is not a requirement. Feature selectivity filters at any level comprise essentially the same operations as are here termed contrast enhancement. Of particular interest in the olfactory system are the potential contrast enhancement capabilities of the external plexiform layer – a deeper layer of the olfactory bulb in which mitral cell secondary dendrites interact reciprocally with inhibitory granule cells and hence indirectly with each other. That is, this layer mediates lateral inhibition among mitral cells, though the pattern of this inhibition does not appear to reflect a two-dimensional center-surround architecture [8,9]. While it has been argued that this processing layer lacks the full complement of afferent information necessary to mediate contrast enhancement with respect to physical stimulus attributes [3,4], it appears architecturally capable of manipulating high-dimensional stimulus representations, and hence of mediating feature-selective operations on odor representations using arbitrary scales and masks that are not constrained by the externally-defined odotope similarity metric. For example, these masks may reflect prior odor experience and olfactory learning and could contribute to complex processing such as the binding of multiple structurally-unrelated odorant features into unitary odor percepts. However, while the circuitry and synaptic interactions within this layer are clearly plastic and responsive to odor learning [10], the function of this post-glomerular circuitry remains unclear.

Contrast enhancement is a general term for what might in retrospect be more broadly referred to as selective feature enhancement, and is a ubiquitous process in sensory systems. While the operational principles are common across sensory modalities, the basic properties of the olfactory modality necessitate underlying mechanisms for contrast enhancement that are dissimilar from those operating in other sensory systems. Neuromodulatory regulation of receptive field stringency in second-order olfactory principal neurons, and the plasticity of bulbar circuitry in response to olfactory discrimination learning, identify these contrast enhancement mechanisms as a crucial part of the adaptive plasticity of an active sensory system.

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Contraversive

Definition

Directed toward the contralateral side.

Control

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Definition

Control is a generic term used to describe the process of acting on a system to cause it to behave in some

desirable fashion [1,2]. A control system typically comprises of four components. These are the physical system to be controlled, ►sensors used to measure the current behavior of the system, ►actuators used to apply "forces" to the system to affect its behavior and an associated algorithm that commands the actuators. A typical control system combining these four components is shown in Fig. 1.

The "control law" in Fig. 1 can often be further decomposed into a "feedforward" component and a "►feedback" component as shown in Fig. 2.

Description of the Theory

Control design consists of designing the algorithm. Typically, the algorithm uses both the desired behavior and the output of the sensors. The latter provides feedback of the current behavior.

Control systems appear in many areas including biology, industry, economy, etc. Three illustrative examples are:

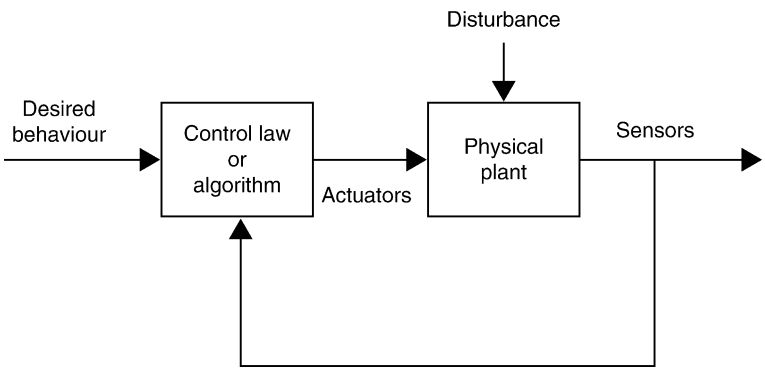
1. In biology: We sense using our eyes; we use our hands as actuators and our brain implements the algorithm.
2. In automobile cruise control: We sense vehicle speed; we use the throttle as an actuator to cause the engine to deliver torque to the wheels that, in turn, changes the speed. The algorithm is typically implemented in a small on-board computer.
3. The human heart: This is an example of a complex biological control system with multiple interacting sensors and actuators that are part of the autonomic nervous system [3]. Actuation occurs via the parasympathetic and sympathetic nervous system. The former can release acetylcholine, which slows the rate of the heart whilst the latter can release noradrenaline, which can speed-up the heart beat. Blood flow to individual tissues is regulated by local control systems in a cascaded structure. When the overall demand exceeds the capacity of the pulmonary circuit then outer control loops come into play. Sensors measure O_2, CO_2 and pH (via chemical receptors) and blood pressure (via stretch receptors).

The central nervous system uses this information to control breathing, heart rate and blood flow via "feedback" control systems. There also exist "feedforward" components, which respond to emotions and anticipation of future activity (flight or fight).

Control has a long history [4] in engineering, beginning with windmills that automatically pointed into the wind and clocks that regulated their speed. A boost to control theory occurred during the industrial revolution when steam power was harnessed to drive engines used in textiles and other manufacturing enterprises. A well-known invention from that period was the fly ball governor [4], which was a mechanism to regulate the speed of a steam engine under different load conditions. Referring to Fig. 1, in the fly ball governor, the engine speed was sensed by two fly balls that were thrown outwards by centripetal forces as the engine rotated. This action was connected via a system of levers (the "algorithm") to a throttle valve (the actuator) which changed the flow of steam to the engine. The basic idea of this device was that, if the engine sped up, the fly balls would swing out and this would cause the throttle valve to close, thus delivering less steam to the engine thereby causing it to slow down, i.e., to return to the desired engine speed. One can well imagine that feedback mechanisms of this type can sometimes fail to yield satisfactory behavior. In particular, if the adjustments to the throttle are too large in comparison with the changes in speed, then one can obtain self-sustaining oscillation, or worse, the system can shut down or over-speed. Thus, science is needed to design the feedback gains so that the system operates properly.

States, Controllability, Observability and Stability

Four key concepts that arise in the context of control are those of "►state," "►controllability," "►observability," and "►stability" [1]. These ideas are briefly described below.



Control. Figure 1 Control system.

The current state of a system describes the values of those variables, which together with the future inputs to the system uniquely define the subsequent response [1,5]. Thus, we sometimes loosely talk about the "state" of the economy. In engineering systems, the state is often a way of summarizing the current internal energy of a system. The state will typically consist of a multidimensional vector of quantities. Obviously, knowing the current state of a system is extremely helpful in determining what input trajectories to apply (via the actuators) to cause the subsequent response of the system to correspond to some desirable behavioral pattern.

In some cases, one has enough sensors available to measure the full state vector. This is the most desirable situation for a control system. In other cases, the available sensors will only give direct information about a sub-set of the states. However, by observing the available sensor data over a non-infinitesimal time internal, one can sometimes reconstruct (or calculate) the current state vector. If this is possible, then we say that the system is "observable" from the given sensors [5,6]. The property of "observability" has been well studied. For simple systems (i.e., those exhibiting linear time invariant behavior), simple ways exist of testing a model to see if it is observable for the given sensors [1,5].

A related question is the following: Say we know (or can estimate) the current state, does a sequence of input changes exist over a future time period (a few minutes, hours or days), which we can apply via the actuators to cause the state to go from its current value to some desirable value. This property is called "controllability" [5,6]. We say that a system is controllable (using the given actuators) if the state can be taken from one point to another. Obviously, controllability is a highly desirable property. We only need to think of the problem of dieting, i.e., does a program of food consumption exist that will cause our body's state (weight, cholesterol levels, sugar levels, resting blood pressure) to go from some given initial value to some desired final value over a given period of time. Controllability is a very well studied question. For simple systems (i.e., those exhibiting linear time invariant behavior), simple ways exist of testing a model to see if it is controllable from the given actuators [1,5].

One may imagine that controllability and observability are important properties of a system. Indeed, many of the standard methods for control system design depend on the satisfaction of these core properties for their success [6,7].

Another core property of dynamical systems is that of stability [1,2]. A system is said to be stable if it returns to some equilibrium condition after it is perturbed. A system that is not stable can either oscillate or exhibit divergent behavior. We say that a physical system is "open-loop stable" if it is stable when considered in isolation. We say that a feedback control system is "closed-loop stable" if the full control system acts in a stable fashion with the controller attached.

Feedback can be used to turn an open-loop unstable system into a stable closed-loop system. However, feedback, if inappropriately applied, can also have the contrary effect, i.e., feedback can lead to instability if the gains around the loop are too high. For example, readers may have experienced the high-pitched whistling sound that is often heard in concert halls when a high gain feedback loop is inadvertently formed from the loud speakers to the microphone and back to the speakers through the audio amplifiers. This is an example of an unstable feedback loop. This behavior is generally highly undesirable (unless one is deliberately trying to produce an oscillation). A notorious example of an unstable control system was the circumstances that led to the Chernobyl explosion. In engineering feedback control systems, one usually makes stability a major design objective.

Internal Models in Control

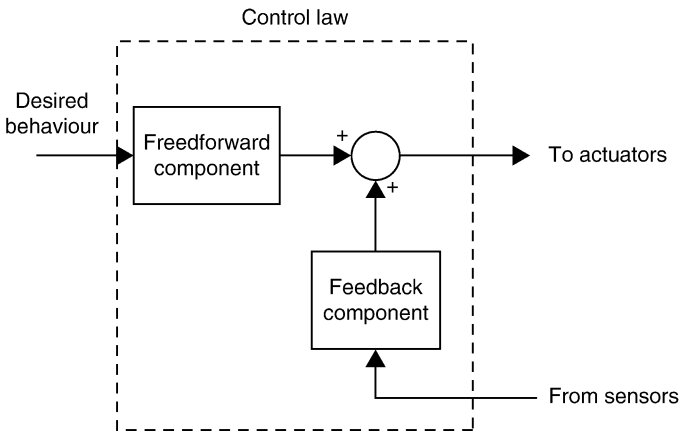
Readers are referred to the companion article on "internal models." For simple cases (e.g., systems that are open-loop stable and have linear time invariant dynamics) it can be shown that all control laws that yield a stable closed-loop must explicitly or implicitly contain an internal model of the system. Indeed, it can be shown that for the simple case referred to above, all stabilizing linear control loops can be redrawn as in Fig. 3, [1,8]. The components inside the dotted line in Fig. 3 represent the control law shown in Fig. 1. In this context, the art of control system design amounts to choosing the contents of block 1 and 2 in Fig. 2. These blocks typically contain a "good" approximation to the inverse of the model, where the term "good" at a minimum includes the fact that block 1 and block 2 must be stable when considered in isolation. Typical control system design methods described in the engineering literature (H∞, LQG, etc.) [1,6,7] are basically algorithms for choosing block 1 and block 2, so that they are good "approximations" to the inverse of the model (where "good" is measured by some specific criterion).

Thus, control laws also contain approximate "inverse models" [1].

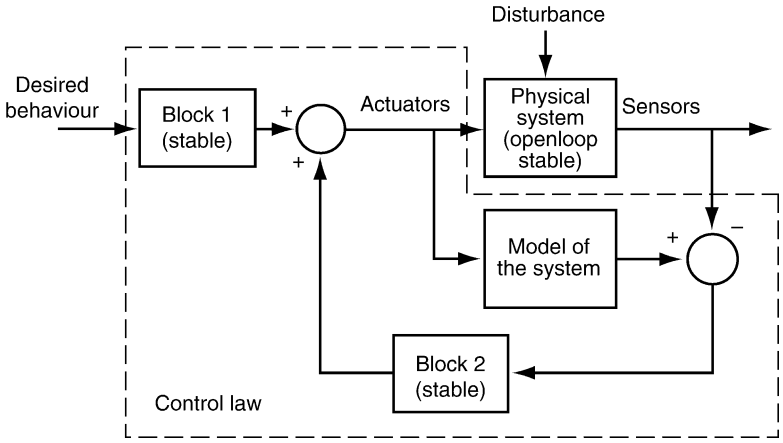
Further Properties of Control Systems

As mentioned above, closed-loop stability is a core requirement of most feedback control systems. Other desirable properties are as follows (here we refer to Fig. 3):

1. Insensitivity of the output response to errors in the model of the system



Control. Figure 2 Decomposition of control law into feedforward and feedback components.



Control. Figure 3 The control law in the Internal Model form.

2. Insensitivity of the output response to disturbances
3. Insensitivity to errors in block 1 or block 2

The feedforward component of a control law (see Fig. 2) is maximally sensitive to errors in the model, since its behavior is predetermined without "seeing" what actually happens. On the other hand, the feedback component of a control law (see Fig. 2) usually has reduced sensitivity, since the control actions (as applied to the actuators) are moderated by what actually happens (i.e., the sensors give immediate "feedback" on what is actually happening).

Indeed, one of the principal advantages of feedback is that it helps achieve reduced sensitivity [1]. In particular, provided closed-loop stability is retained, then output sensitivity typically decreases proportionally to the loop gain. (i.e., the product of all gains around the loop). The most common control law used in industry is a Proportional-Integral-Derivative (PID) controller [1,2,4]. These controllers have a key property in that they have infinite gain in steady state (due to the integral term). Hence, the output response is total insensitivity to steady state disturbances when a PID controller is employed.

Fundamental Limitations for Control Systems

In common with all physical systems, feedback control systems are subject to fundamental limitations, i.e., there are some things that just cannot be achieved based on the available sensors and actuators [9]. Issues that limit the achievable performance include:

1. Actuator amplitude limits and slew rate limits, i.e., there is usually a maximum input that can be applied and a maximal rate that an input can be changed [10].
2. Time delays in the sensor system – if the sensors give us "old data," then we need to be very careful in applying large corrective forces via the actuators, since the system may have "moved on" making the

data from the sensors obsolete and hence potentially destabilizing [9].
3. Inverse response – many systems have the annoying property that they initially respond in the wrong direction. Inverse response limits how quickly a system can be forced to respond, since the magnitude of the response in the wrong direction typically increases as one tries to move the system faster [9]. (The reader can check this claim by balancing a stick on his/her hand. First notice that this system exhibits an inverse response, i.e., if you want to move the balancing position left then you must first move to the right. Also, notice that the faster you try to go left then the further you need to go in the inverse direction.)
4. Modeling errors, i.e., errors between the true system dynamics and the dynamics as captured in the "model." Errors of this type will eventually lead to closed-loop stability being lost [7], since the control law implicitly takes for granted that the model is correct.

Unfortunately, biological and engineering systems often have the property that their characteristics change due to external influences (e.g., slow changes due to aging or more dramatic changes due to surgery or other interventions). For small changes, the control loop will continue to give satisfactory behavior due to the inherent capacity of feedback to adjust the inputs applied via the actuators to correct errors as seen by the sensors. However, for large changes in the system (i.e., major changes in the dynamics or gains), the control system may begin to exhibit erratic behavior including instability. In such cases, one needs to adjust the internal model used in the control system so that it better approximates the current system characteristics. This leads to the idea of an "adaptive controller" (see companion article).

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Control System

►Feedback Control of Movement

Control Theory

►Modeling of Human Postural Control

Control Treatment

►Placebo Analgesic Response

Control Variables (CVs), also Central Commands

Definition

Neurophysiological parameters that, depending on the motor task, may be kept constant or changed by the nervous system; can be specified independently of state variables; effectively influence the latter thus producing intentional motor actions; represent different forms of threshold control.

►Equilibrium Point Control

Controllability

Definition

Controllability represents the ability to affect physical system behavior by means of the actuators connected to

it. In terms of system states, it is the ability to move the system from one arbitrary state to another.

►Control

Controller

Definition

The device which controls the plant.

►Neural Networks for Control

Contusion

Definition

A "brain bruise." Injury occurring as a result of the brain colliding with the boney and dural surfaces of the skull. Pathologically contusion corresponds to the area of hemorrhagic necrosis on the surface of the cortical gyrus. The severity of the contusion depends on the location as well as mobility of the head during the impact. If the head is injured while immobile, the focus of the primary injury will be located at the impact site, a so called "coup" injury. When the head is struck while moving, the majority of the contusion may be located on the opposite side of the head from impact, a "contra coup" injury. The contusions are most frequently seen on the subfrontal and anterior temporal cortical surfaces, partly due to irregular architecture of the interior of the skull in these areas.

Contusion Injury

Definition

Spinal cord bruising initiating death of spinal cord cells, loss of spinal tissue.

Contusion Injury Model

Definition

Contusion injury model is a model of spinal cord injury (SCI) created in animals by bruising the spinal cord. It is usually made by dropping weights from certain heights or by mechanically applying a certain force. The pathophysiology of contusion injuries is rather similar to that of SCI in humans. Other SCI models that have been established are the transection model (complete transection of the spinal cord), and the hemisection model (half cut model), etc.

Convergence Neurons

►Near Response Neurons

Convergent Eye Movement

Definition

Adduction of the eyes to view a nearer target.

Conversion Disorder

►Hysteria

Convex Hull

Definition

In two-dimensional systems, a minimum convex polygon.

►Evolution and Brain-Body Allometry

Convolutions

Definition

The gyri and sulci ("hills and valleys") of the cerebral cortex.

►Evolution of the Brain in Humans – Paleoneurology

Convulsant Drugs

Definition

Group of drugs, which can induce ►seizures. These drugs include antagonists of ►glycine receptors (e.g., strychnine) and antagonists of the ►$GABA_A$ receptor (e.g., bicuculline and picrotoxin).

►GABA
►Glycine

Coordinate Systems for Head Rotations

Definition

Head angular rotations are usually described as rotations about cardinal axes. Rotations about the vertical axis are called yaw, those about the interaural axis pitch and those about naso-occipital axis roll.

Coordination

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The Pensylvania State University, University Park, PA, USA

Synonyms

Dexterity; Skill; Adroitness; Synergy

Definition

The word "coordination" is used in two general meanings. First, as an ability to perform motor tasks in an efficient way (synonymous to dexterity or skill, e.g., "your child has good coordination"). Second, as a purposeful pattern of actions by a set of effectors (synonymous to ►synergy, e.g., "hand function depends on coordination of the digits"). Coordinated motor patterns have been viewed as resulting from an action by the central nervous system (CNS) confronted by the problem of *motor* ►*redundancy*, also known as the ►*Bernstein problem* [1,2], and constrained by factors related to the environment and the body mechanics [3]. Redundant motor systems can be described with elemental variables (►degrees-of-freedom, DOFs) whose number is larger than the number of constraints imposed by typical motor tasks. Theoretically, such systems have an infinite number of solutions for specific motor tasks. Two major views on the origin of motor patterns observed in redundant systems have dominated the studies of motor coordination. First, that coordination results from elimination of the redundant DOFs by the CNS [1], possibly based on certain optimization criteria. Second, that no DOFs are ever eliminated, but they are all used to stabilize particular performance variables – the principle of ►abundance [4]. According to the latter view, coordination within multi-element systems has been assumed to result from organizing elements into *synergies*, defined as particular neural organizations of elemental variables that stabilizes a required value or a time profile of important performance variable(s). Within the ►*dynamic systems* approach, coordination has typically been viewed as a particular stable phase relation between actions of a set of effectors [2,5].

Characteristics

Quantitative Description

Coordination has been notoriously hard to quantify, largely because of the lack of agreement on what constitutes coordination. In recent studies, coordination (synergies) has been quantified using measures of stability of motor patterns commonly applied to analysis of cyclic actions within the *dynamic systems* approach to movement studies [5], principal component analysis, comparison of actual and surrogate data sets created using patterns of elemental variables selected randomly from different attempts at a task [6], and analysis of co-variation of elemental variables within the framework of the ►uncontrolled manifold (UCM) hypothesis [7]. Within the last approach, variance in the state space of elemental variables is quantified within a subspace (a UCM), corresponding to a certain value of a hypothetically important performance variable and orthogonal to that subspace. Comparing the two variance magnitudes per DOF within each subspace allows to conclude whether the elemental variables are coordinated to stabilize the performance variable. This method has been used to quantify coordination in healthy young persons performing various motor tasks, as well as atypical coordination in special subpopulations, such as persons with Down syndrome, healthy elderly, and patients after stroke. It was also used to track changes in coordination that occur with practice.

Higher Level Structures

Coordination is a complex phenomenon that probably cannot be associated with a single neural structure or a subset of neural structures. Cerebellum has been traditionally viewed as a brain structure directly related to motor coordination [8], partly based on observations of impaired coordination in animals with cerebellar

lesions and patients with cerebellar disorders. However, coordinated limb movements can be observed in animals without the cerebellum, and even in animals whose spinal cord is surgically separated from the brain. Typical examples include spinal locomotion, wiping reflex, and scratch reflex. Apparently, different parts of the CNS are able to produce coordinated motor actions, and the natural coordination in intact animals is a result of a combined action of numerous structures within the CNS. This conclusion is indirectly supported by observations of impaired coordination in cases of virtually all neurological disorders.

Lower Level Components

Coordinated action has been studied for groups of elements at different levels of description of the human behavior. Most studies of motor coordination analyzed it at the level of muscle interaction, joint interaction, or effector interaction during complex actions such as locomotion, vertical posture, ►prehension, and speech. However, coordination of motor actions at "higher" (inter-personal coordination, e.g., coordinated actions of players of a football team) and "lower" (e.g., coordination of motor units within a muscle) levels has been addressed. One of the most influential hypotheses of motor control, *the* ►*equilibrium-point hypothesis* [9], may be viewed as being associated with establishing a coordination law that stabilizes equilibrium states of the neuromotor system comprised of the organism and environment. According to this hypothesis, the CNS parametrizes the neuromotor system, and synergies emerge following the natural tendency of the system to reach a steady-state.

Higher Level Processes

Coordination may be viewed at levels that transcend the motor function. In particular, grammar may be viewed as coordination of words within a language, interpersonal interactions may be viewed as governed by coordination laws, and even the world economy may be viewed as resulting from a (poorly) coordinated action of local economies. Studies of autism have suggested that this state may be associated with a disruption of coordination at a basic level reflected in impaired inter-personal, language, and motor abilities, possibly causally related to changes in the cerebellar function.

Lower Level Processes

Coordination has typically been studied as relations within a set of variables (elements, effectors) selected by researchers, largely based on common sense and intuition. There is no unambiguous definition for an elemental variable. Depending on the level of analysis, elemental variables could be related to outputs of individual motor units, muscles, joints, limbs, digits of the hand, speech articulators, persons, etc. Elemental variables can be characterized by a certain irreducible level of variability in their outputs. Coordination of several elemental variables implies that they contribute to a common task in a certain way (sharing), and deviations of their outputs from a preferred pattern co-vary to stabilize a pattern of an important task-related variable (error compensation). Correspondingly, synergies can be characterized by two indices related to sharing (relations among average patterns of elemental variables) and error compensation (relations among dispersions of elemental variables across several attempts at the same task). Variability of elemental variables may be viewed as consisting of two components, one of which affects a selected performance variable ("bad" or non-goal-equivalent variability) while the other does not ("good" or goal-equivalent variability). Synergies stabilize performance variables by making most of the variability of elemental variables "good." Several performance variables may be stabilized simultaneously if a sufficient number of elemental variables are available. For example, studies of digit coordination during human prehension has shown the existence of at least two synergies (null-spaces) related to grasping the object with sufficient strength and ensuring its rotational equilibrium.

Process Regulation

Task-specific co-variation of elemental variables, which stabilize important performance variables, may be viewed as a process of formation of corresponding null-spaces within the space of elemental variables by the CNS, and channeling most of the variability into the null-spaces. Neural processes participating in the formation of such null-spaces are unknown. An optimal feedback control mechanism has been suggested to ensure stabilization of performance variables by coordination of elemental variables [10]. Coordination can also be based on central back-coupling mechanisms, using efferent copies of outputs of neural elements directly related to elemental variables. Possible involvement of different neural structures including the spinal cord, the cerebellum, and the cortex of the large hemispheres into regulation of coordination has been documented using electrophysiological methods and brain imaging techniques. Developmental studies have shown that elements of motor coordination exist immediately after birth, but much of the repertoire of human coordinated actions is discovered by the CNS over the first months and years of life. Practice is a commonly used method to improve coordination or develop new coordinated actions. A decline in motor coordination is seen with advanced age.

Function

Coordinated movements are expected to show two features that seem hardly compatible: Stability of performance in the presence of unavoidable unpredictable

changes in the environment and within the neuromotor system, and flexibility of performance in cases of quick modifications of the task and/or major changes in external conditions. The former aspect of coordination has dominated movement studies. Correspondingly, coordination has been frequently quantified using indices that describe stability of the system's behavior [5]. However, coordinated actions may be purposefully organized to destabilize aspects of motor behavior if the context requires quick modifications of important performance variables. Coordination may also have, as a goal, a perceptual effect (as in some sports such as figure skating and synchronized swimming) or a complex perceptual-motor effect that cannot easily be formalized (as in a stretching exercise).

Pathology

Virtually all motor pathologies lead to problems with motor coordination. In particular, impaired coordination has been described for movements of patients suffering from cerebellar disorders, Parkinson's disease, systemic neurodegenerative disorders such as multiple sclerosis, peripheral disorders including peripheral neuropathies and myopathies, after stroke affecting the large hemispheres, and after spinal cord injury. Impaired coordination is also seen in atypically developing persons, such as those with cerebral palsy, Down syndrome, and with the Developmental Coordination Disorder, as well as in healthy elderly. Some of the changes in motor coordination may be viewed as adaptive to a pathology and optimal for the actual state of the person's central nervous system and the peripheral neuromotor apparatus.

Therapy

Disorders of motor coordination have been notoriously difficult to correct. Pharmacological and invasive therapies (such as surgery and implantation of stimulators) typically address more basic and severe consequences of motor disorders including excessive involuntary movements (tremor, spasticity), weakness, inability to initiate actions, etc. Attempts to treat discoordinated movements, in particular those observed in patients with dystonia, chorea, and cerebellar disorders have been largely unsuccessful. Physical and occupational therapy have been treatments of choice for coordination disorders. Along somewhat different lines, there has been substantial progress in the development of prosthetic devices such as artificial hands. However, these devices have a limited repertoire of possible actions that are marginally coordinated. The current superficial level of understanding of the neural mechanisms of coordination, has not yet allowed the development of prosthetic devices that would be controlled by the person's CNS, based on the same principles as it uses to control natural actions.

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Cordotomy

Definition

A surgical lesion of the anterolateral funiculus used in terminal patients with intractable pain. Prevents nociceptive signals from ascending to the brain by cutting the spinothalamic and other nociceptive pathways.

►Ascending Nociceptive Pathways

Core and Shell SCN

Definition

The suprachiasmatic nucleus (SCN) of hamsters, mice, rats and humans is comprised of two fundamentally different regions based on cell size, peptidergic phenotype and morphology, afferent and efferent connections, and patterns of expression of clock genes. The relationship between these two subdivisions is quite consistent among mammalian species. The core

lies closest to the optic chiasm, and the shell largely surrounds the core. The older term for core was ventrolateral and for shell it was dorsomedial. This terminology was based on studies on the rat, where these geographical locations held true. In other species, the SCN still has at least two distinctly different regions, but their location in space may differ from that of the rat, giving rise to the need for new descriptors.

►Suprachiasmatic Nucleus

Corollary Discharge

Definition

A term coined by Roger Sperry in 1950, who studied the opto-motor response in fish. It states that any eye motion that will cause displacement of the visual image on the retina will have "a corollary discharge into the visual centers to compensate for retinal displacement." This allows the animal to determine whether image motions on the retina were caused by movements of the object or by eye movements of the animal itself. The same principle was simultaneously and independently discovered by Erich von Holst and Mittelstaedt termed "efference copy." Specifically, the term refers to internal neural correlates of the descending motor command that are involved in the perception of force and in the decoding of muscle spindle responses. Also, in mormyrids, the electric organ corollary discharge (EOCD) is an internal reference of the timing of electric organ discharge (EOD) production.

►Auditory-Motor Interactions
►Proprioception: Role of Muscle Receptors
►Reafferent Control in Electric Communication

Corollary Discharge Feedback

►SC – Local Feedback

Corpora Quadrigemina

►Inferior Colliculus

Corpus Callosum

Definition

The largest commissure of the brain. Connects the two halves of the cerebrum and forms the floor of the longitudinal fissure of cerebrum. Consists of four parts: splenium, trunk, genu and rostrum.

►Telencephalon

Corpus Striatum

Definition

Corpus striatum denotes a heterogeneous collection of several deep telencephalic nuclei, including the caudate nucleus and putamen, which receive massive outputs from the cerebral neocortex and projections from some subcortical structures and the globus pallidus, to which the caudate and putamen project. The globus pallidus itself projects to a number of sites having to do with motor control, including the brainstem reticular formation and via a relay in the thalamus, motor staging areas of the cortex. Although properly including a number of additional structures, such as the amygdala and septal nuclei, the term basal ganglia is conventionally used to denote the corpus striatum and a number of related structures, such as the substantia nigra and subthalamic nucleus, said to comprise the extrapyramidal motor system. Damage to the corpus striatum results in the typically manifest symptoms of chorea, due to disinhibition of the globus pallidus and substantia nigra. Chorea is characterized at an advanced stage by hyperkinesia especially of the distal extremities' musculature and of the face. Dystonic syndrome (e.g., retrocollis, spastic torticollis) or athetosis are also encountered.

►Basal Ganglia
►Striatopallidum
►Telencephalon

Corpusculum Lamellosum

►Pacinian Corpuscle Regeneration

Corpusculum Tactus

►Meissner Corpuscle Regeneration

Corrective Saccades

Definition

These eliminate the remaining error relative to a target position after a primary, main saccade aimed at this position has failed to bring the eye close enough for foveal vision (error due to open-loop nature of saccades). Corrective saccade occur within approximately normal visual latency (200 ms) upon the end of the primary saccade if the error is small (≤3°) but can be much prompter (130–150 ms) with large errors. If the error is large, corrective secondary saccades can also occur in the absence of visual feedback (target invisible after primary saccade). These characteristics are attributed to the intervention of a non-visual feedback mechanism which, being less precise than visual signals, would be effective only with large errors.

►Oculomotor Control Saccade, Saccadic Eye Movement

Correlation

Definition

A linear measure of the association between two variables. Note that correlation does not imply causation. Correlation between a variable at a certain time instant and itself at other time instances is known as the auto-correlation, while the correlation between two variables is known as the cross-correlation.

►Signals and Systems

Correlation Dimension

Definition

Measure of the size of the attractors in a system. This measure is used to typify the complexity of chaotic systems.

►Signals and Systems

Correlational Research

Definition

An approach, which compares psychophysical and neuronal correlates of sensory performance on a quantitative, descriptive level, by establishing a correlative rather than a material or causal relationship between mental and brain processes. Correlation research was first established in the study of vision by Richard Jung and co-workers and has meanwhile become an established venue of research in modern neuroscience.

►Psychophysics

Correlative Neuroanatomy

►Functional-Anatomical System

Cortical

Definition

Related to the cerebral cortex, the outermost layers of the brain.

Cortical Areas

Definition

The cerebral cortex in primates is divided into a large number of areas based on criteria such as cyto-, myelo- and/or chemoarchitecture, topographical organization, input-output and intracortical connections, electrophysiological properties of neurons and deficits resulting from local lesions or deactivation (Extrastriate visual cortex). Brodmann's (1909) classification of human cortical areas (Fig.1) is based on cyto- and myeloarchitecture. Von Bonin and Bailey's (1947) classification for monkeys is cruder than Brodmann's (1909) and names areas first according to their location in one of the major lobes (F, frontal; P, parietal; O, occipital;

T, temporal). The subsequent letter has no specific significance, but is one of the initial alphabetic characters. This scheme has been refined and led to further differentiations including, for example, anatomical designations such as "a" for anterior, "c" for caudal etc. For instance, "PGa" denotes the anterior portion of PG (area "G" in the parietal cortex), which is situated rostral to the lateral (Sylvian) fissure close to its posterior end, etc. Some areas are simply designated according to their form or anatomical location, e.g. AIP = anterior intraparietal, or according to their function, e.g. primary motor cortex (MI, M1). Unfortunately, these diverse nomenclatures are often used interchangeably, such that, e.g. Brodmann's area 17 = striate cortex = primary visual cortex = area V1, or Brodmann's area 4 = MI = F1.

Cortical Atrophy

Definition

Cortical atrophy refers to a number of neurodegenerative disorders of the ►cerebral cortex, including syndromes such as ►Alzheimer's disease, ►corticobasal degeneration, ►frontotemporal dementia, ►primary progressive aphasia, ►posterior cortical atrophy.

►Alzheimer's Disease
►Corticobasal Degeneration
►Frontotemporal Dementia
►Posterior Cortical Atrophy
►Primary Progressive Aphasia

Cortical Development

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Synonyms

Cerebral cortex development

Definition

Cortical development typically refers to the process by which the cerebral ►cortex is formed in mammals. The development of the cerebral cortex shares some common features with other cortical structures, such as the cerebellum. However, some aspects of the development of the cerebral cortex are unique to this structure, the highest-order processor of neural function. Cortical development comprises several consecutive phases, which may temporally overlap to a certain extent: induction, patterning, neuronal migration, formation of axonal connections and functional maturation.

Characteristics

Higher Level Structures

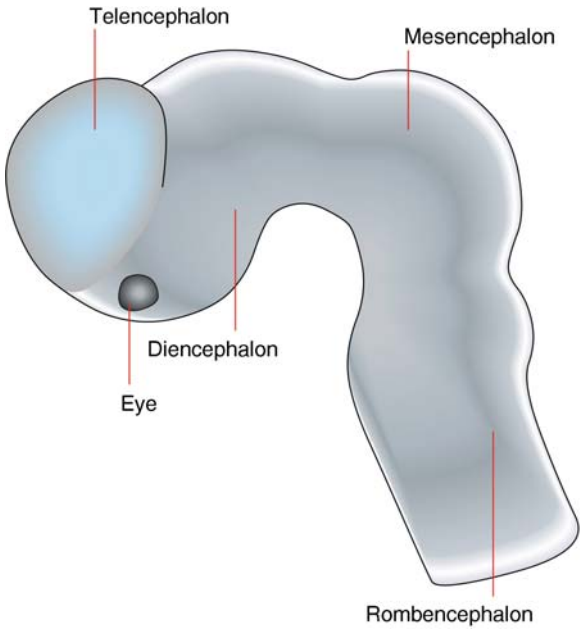
The cerebral cortex develops from the dorsal region of the most anterior vesicle of the neural tube, the prosencephalon or ►forebrain (Fig. 1).

The anlage of the cortex, also known as the ►pallium, is organized in four main radial subdivisions, the medial, dorsal, lateral and ventral pallium [1]. All pallial domains form cortical structures (e.g. superficial laminar neuronal zones), but the lateral and ventral pallium parts also give rise to deep-lying nuclear structures, integrated in the claustro-amygdaloid complex. Hence not all derivatives of the pallium are part of the cerebral cortex. The medial pallium forms the hippocampal complex and subiculum; the dorsal pallium generates the ►mesocortex and the ►isocortex (also less appropriately known as neocortex); finally, the lateral pallium and ventral pallium are thought to give rise to the primary olfactory cortex, the dorsolateral claustrum and parts of the amygdala (basolateral nucleus, amygdalo-hippocampal area) and periamygdaloid cortex. The lateral pallium and the medial pallium fuse together around the dorsal pallium, forming the allocortical ring around the meso- and isocortex.

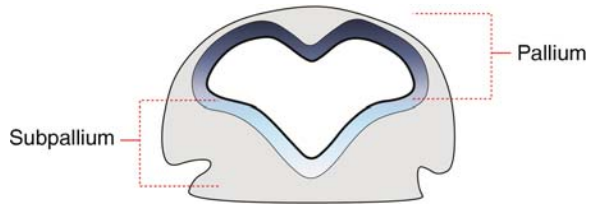
The distinct types of cortices are characterized by specific morphological features, among which the number of layers is the most distinctive. The hippocampus and the olfactory cortex consist of three layers each, whereas the isocortex is typically made of six layers. The axonal connections formed by different layers of the cortex are also different. For example, layer II-III pyramidal neurons form connections within the cortex, whereas layer V and layer VI target subcortical structures.

Lower Level Components

The cerebral cortex contains two major classes of neurons, glutamatergic pyramidal cells and γ-aminobutyric containing (GABAergic) interneurons. The majority of cortical neurons are pyramidal cells (~80%), which are responsible for establishing long connections between different cortical areas and between the cortex and other subcortical regions (pyramidal cells are also known as cortical projection neurons). Interneurons, on the other hand, constitute a rather heterogeneous group of neurons responsible for establishing local circuits in the cortex.



Cortical Development. Figure 1 Schematic representation of a lateral view of the brain of a mouse embryo at around embryonic day 10, showing its main subdivisions.



Cortical Development. Figure 2 Schematic representation of a coronal section through the embryonic day 10 mouse telencephalon, in which the pallial and subpallial domains are delineated.

Higher Level Processes

As the cerebral cortex forms from the most anterior region of the neural tube, its development requires first the acquisition of anterior neural character in a process that involves signals emanated from the ►node and the anterior visceral endoderm. Since the anterior character is the default state of the early neural plate, inhibitors of factors that induce a posterior character are responsible for maintaining anterior neural identity. Additional patterning events specify within the anterior neural plate the territory occupied by the telencephalon, from which the cortex develops. This second patterning process requires signals from the anterior neural ridge, a group of cells located at the junction between the anterior neural and non-neural ectoderm. Subsequently, a dramatic set of morphogenetic movements accompanied by extensive proliferation lead to the transformation of the anterior neural plate into a set of paired vesicles. In parallel to this process, patterning events driven by the dorsal midline and the ►prechordal plate regionalize the telencephalon into distinct ventral (►subpallium) and dorsal (pallium) domains, with the later giving rise to the cerebral cortex (Fig. 2).

Such signaling centers lead to the induction of a combinatorial code of homeodomain and bHLH transcription factors within progenitors at different dorsoventral positions of the telencephalon [2]. In the pallium, this code defines the emergence of at least four distinct territories (ventral, lateral, dorsal and medial pallium), which will eventually give rise to different types of cortices.

Cortical projection neurons and interneurons follow largely different developmental programs [3]. In short, projection neurons originate throughout the ventricular zone of the different pallial regions and migrate radially to form the different types of cortices. Interneurons, on the other hand, originate in the ventricular zone of the subpallium and migrate tangentially to the pallium, where they eventually change their mode of migration to settle in specific layers of the cortex. Cell layers within the cortex are generally established according to an inside-out pattern. Accordingly, projection neurons produced simultaneously migrate and stop migrating roughly at the same time, so they all occupy the same cortical layer. GABAergic interneurons tend to adopt the same cortical layer as synchronically generated projection neurons, even though interneurons must migrate through much greater distances than projection neurons and thus require additional time to reach the pallium.

Our understanding of the mechanisms underlying the development of the circuitry that confers functional properties on the cerebral cortex is still relatively poor, although much is already known about the development of certain cortical connections, such as the reciprocal thalamocortical pathway. Thalamocortical and corticothalamic projections have to cross several boundary regions to reach their target, including the diencephalic-telencephalic boundary, the ventral telencephalon and the pallial-subpallial boundary. In addition to specific guidance molecules, thalamocortical and corticothalamic axons have been shown to interact with each other, at least at they cross the subpallium [4].

Neuronal circuits in the cerebral cortex are shaped by experience during specific periods of early postnatal life, named critical periods. In the cortex, this activity-dependent development is caused by the functional maturation of local inhibitory connections of specific subclasses of cortical interneurons.

Lower Level Processes

Inhibitors of "posteriorizing" factors, such as the Wnt, BMP or Nodal signaling antagonists Cerberus and

Dickkopf, are involved in the early induction of the anterior neural plate. Other factors involved in the early induction of these territories are Chordin, Noggin and Follistatin. Subsequent patterning events, which define the territory occupied by the telencephalon, also require the inhibition of "posteriorizing" factors (in this case those that induce the development of the diencephalon), including but probably not limited to Wnt signaling. Dorsoventral patterning of the telencephalon largely depends on a balance between "dorsalizing" factors, such as Wnt and BMP signaling, and "ventralizing" activities, mostly Shh. The acquisition of a pallial fate by telencephalic cells involves the expression of specific transcription factors, such as *Pax6* and *Ngn2*. Furthermore, progenitor cells from the different pallial domains also express different combinations of transcription factors [5].

There has been considerable controversy over the mechanisms through which early subdivisions of the cerebral cortex are generated. One school proposed that mechanisms intrinsic to the cortex play a fundamental role in this process (the "protomap" model), whereas another suggested that regional identity is primarily controlled by the nature of thalamic axonal inputs that the different neocortical domains receive. A large body of evidence now supports the "protomap" hypothesis, according to which cues that specify particular areas act on cortical progenitor cells. Some of these cues are beginning to be identified [6].

Migration of cortical projection neurons and interneurons is largely controlled by different factors. Radial migration of cortical projection neurons depends on the Reelin pathway, and may also involve integrin signaling [7]. Tangential migration of cortical interneurons depends on several chemoattractive and chemorepellent molecules, including class III semaphorins, neurotrophic factors and Neuregulin-1 [8].

The development of axonal connections in the cerebral cortex involves multiple chemoattractive and chemorepellent molecules. For example, development of the corpus callosum requires Netrin-1, whereas the formation of corticofugal projections arising from layer V and layer VI neurons relies on Slits [9].

Pathology

Disturbances of the inductive events involved in primary neurulation result in various errors of neural tube closure. Failure of anterior neural tube closure leads to anencephaly, which commonly involves the forebrain and variable amounts of upper brainstem. Defects in the formation of the forebrain at the rostral end of the neural tube range from the complete absence of the entire prosencephalon (aprosencephaly) or telencephalon (atelencephaly) to relatively mild disturbances of midline prosencephalic development (e.g. agenesis of the corpus callosum). Severe deviations from normal prosencephalic development may also involve defects in prosencephalic cleavage that typically lead to holoprosencephaly, a condition in which the telencephalon develops as a single spherical structure.

There are multiple neuronal migration disorders in humans that affect the developing cerebral cortex. Because neuronal migration in the human cerebral cortex extends through a protracted period of time, typically between the 11th and the 24th weeks of gestation, the spectrum of migration disorder severity may extend from only a reduced number of heterotopic neurons, as observed in periventricular heterotopia, to complete laminar disorganization, as described in severe cases of lissencephaly. Nevertheless, migration disorders of the cerebral cortex are responsible for a large percentage of cases of mental retardation and epilepsy in children.

Despite making up a small percentage of the entire neuronal population, the activity of GABAergic interneurons is critical for cortical function, as they represent the basic elements that provide inhibition, synchronize and shape several types of cortical oscillations underlying various brain functions. Several lines of evidence suggest that abnormal development of GABAergic interneurons may underlie the development of important neurological disorders, from epilepsy and learning disabilities to schizophrenia [10].

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Cortical Development – Disorders

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Definition

Being discussed will be major disorders of cortical development: malformations arising from abnormal neural tube closure, congenital midline defects, abnormal neuronal proliferation and migration, and disorganized lamination and convolution. These severe disorders are associated with neonatal death or mental retardation and epilepsy.

Characteristics

The ►neocortex originates from a very small population of ►stem cells. Through different phases of progenitor (►Neuronal progenitor) expansion and migration, these cells eventually form the six neuronal layers of the human neocortex. Genetic analysis of human disorders have highlighted various types of proteins that are critical for proper cortical development. Given the divergent nature and tight spatiotemporal orchestration of this complex process, early disruptions can cause aberrant progenitor expansion, migration or ectopic placement of neurons and produce severe malformations.

Early Brain Development

Brain development is a complex and tightly controlled process (ERNS Chapter by Marin, 2008). The cerebral ►cortex consists of an outer layer of heavily interconnected neuronal tissue spanning the entire cerebrum. The human cortex importantly is responsible for many cognitive functions. When its development is disturbed, typically human disorders like aphasia, epilepsy, learning disabilities and mental retardation ensue.

Development of the Neocortex

Neocortical development in the rodent involves the generation of postmitotic ►pyramidal neurons from a very small population of stem cells located in a region called the ventricular zone lining the lateral ventricles of the dorsal neocortex. These stem cells undergo successive phases of progenitor division and ►radial migration to reach their final laminar positions in a so-called "inside-out" manner. Interconnecting with the radially oriented, excitatory pyramidal neurons are GABAergic inhibitory neurons, that originate from the ganglionic eminences and migrate tangentially (►Tangential migration) This results in six heavily interconnected neuronal layers with distinct identities and inputs [1,2] (Fig. 1).

Radial migration is accomplished through ►nuclear translocation and ►locomotion. ►Radial glia cells function as a scaffold enabling guidance of locomoting migratory neurons towards the outer ►pial surface. During early embryonic development migration occurs through glia-independent translocation that is characterized by movement of the soma and nucleus into a long leading process attached to the pial surface [2]. In addition to a role in guidance, radial glia produce almost all radially migrating neurons generated in the VZ. Hence, radial glia are neuronal precursors in corticogenesis [3].

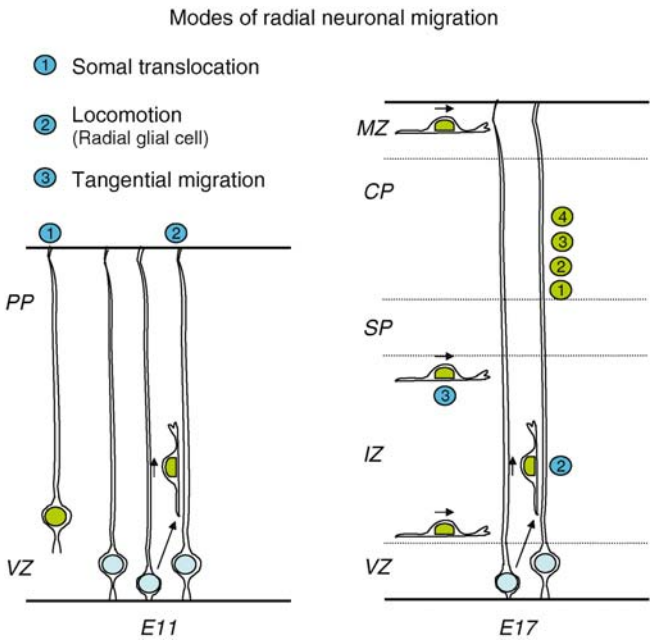
Neuronal Proliferation and Migration Disorders

Despite considerable progress, little is still known about the proteins controlling early cortical development. Various cytoskeletal-associated proteins have recently been implicated in processes like cell division, differentiation and neuronal migration [4] and also in cortical developmental disorders such as microcephaly, lissencephaly and doublecortex syndrome [5,6]. These genes may provide important insights not only into evolutionary aspects of variation in cortical thickness for example, but also into how normal human cortical development is controlled.

Gyrencephaly/Microcephaly

Microcephaly is defined by a reduced head circumference and a significant diminution in brain volume. Microcephaly is divided into primary microcephaly, in which the brain fails to grow to the correct size during pregnancy, and secondary microcephaly, in which the brain is the expected size at birth but subsequently fails to grow normally. Current work suggests that primary microcephaly is caused by a decrease in the number of neurons generated during early ►neurogenesis [7], while in secondary microcephaly the number of dendritic processes and synaptic connections is reduced. Genetic but also non-genetic causes of primary microcephaly occur, such as maternal alcohol consumption during pregnancy, maternal syphilis infection, poor prenatal care and "non-accidental head injury."

Individuals with autosomal recessive primary microcephaly (MCPH) are born with a significantly small head circumference and are mentally retarded. Brain scans show that the whole brain is reduced in size, with the cerebral cortex most severely affected. Four genes that cause MCPH have been identified, microcephalin, abnormal spindle in microcephaly (ASPM), CDK5RAP2 and CENPJ. All of the mutations are predicted to lead to a premature termination of the protein and for ASPM, there



Cortical Development – Disorders. Figure 1 Scheme depicting different forms and directions of neuronal migration during early cortical development. *Abbreviations: MZ* marginal zone; *CP* cortical plate; *SP* subplate; *IZ* intermediated zone; *VZ* ventricular zone; *E11* embryonic day 11; *E17* embryonic day 17.

is no correlation between the position of the mutation and the degree of microcephaly. Indeed nonsense mediated mRNA decay will almost certainly occur for each of these mutations and hence it is the functional absence of the ASPM protein that causes MCPH. ASPM is most probably involved in the organization of microtubules at mitotic spindle poles. Mutations in microcephalin lead to premature chromosome condensation and cell cycle defects. CDK5RAP2 and CENPJ have both been implicated in centrosomal function.

Lissencephaly, Band and Nodular Heterotopia

Another set of proteins appears critical for neuronal migration to specific brain regions. Based on their phenotype, they can be divided in three groups. The first one encodes cytoskeletal molecules that play important roles during initiation and progression of neuronal movement. The second encodes signaling molecules for which homozygous mutations lead to an inverted cortex and a third group encodes enzymatic regulators of glycosylation that appear to delineate where neuronal migration will arrest [8].

Periventricular Heterotopia (PVH)

Periventricular heterotopia (PVH) arises due to X-linked filamin A (FLNA) mutations. Affected females exhibit epilepsy and have visible malformations on MRI, consisting of nodules of heterotopic grey matter situated close to the cerebral ventricles [9]. In this X-linked form of PVH, affected males are rare and usually die *in utero* or at birth. A second gene identified for rarer forms of PVH associated with microcephaly, is ARFGEF2 [9], a vesicle and membrane trafficking protein. In both these forms of PVH, the position of the heterotopic nodules situated close to the region where neurons are generated during development, suggests severely perturbed neuronal migration. FLNA is a well studied actin-binding protein, which also interacts with integrins and other transmembrane proteins. Thus FLNA is likely to play a role in anchoring such proteins to the cytoskeleton. Such functions could be quite consistent with a role in the first steps of neuronal migration, regulating the movement of a neuron along its substrate. However, alternative functions for FLNA have also been proposed. Data from recently described mouse knockout models show no apparent migration defects, but instead abnormal cell-cell and adherens junctions. Heterotopic nodules close to the ventricles in PVH could thus arise by disruption of neuroepithelial cell contacts at the ventricular lining [10].

Lissencephaly/Doublecortex Syndrome

Also falling in the group of cytoskeletal associated proteins, mutations in ►microtubule associated proteins (MAPs) are correlated with lissencephaly [6]. The ongoing process of migration from the ventricular zone to the ►cortical plate is defective in both type I lissencephaly and in double-cortex syndrome

(DCS). Lissencephaly in humans is characterized by a lack of cortical folds on the brain surface (smooth brain) and a thicker cortex consisting of four layers of loosely packed cells with most cortical plate neurons found in the fourth layer. Type I lissencephaly and DCS are caused by mutations in the microtubule binding protein doublecortin (DCX). Neurons expressing a mutated DCX fail to migrate properly. Regulation of microtubule association occurs through phosphorylation that negatively regulates microtubule affinity [11]. Several kinases which phosphorylate DCX have been identified.

Essentially all missense mutations in DCX have been found in the two microtubule-binding DC repeats. In families with DCX mutations, affected males show lissencephaly whereas affected females show an apparently preserved six-layered outer cortex and a subcortical heterotopic band of neuronal tissue located in the cortical white matter (DCS) [5,6,11]. The mechanisms leading to heterotopia formation remain unclear, although since DCX is localized on the X chromosome, X inactivation may well generate such a mosaicism. Individuals with lissencephaly typically display severe mental retardation and intractable epilepsy, whereas individuals with DCS typically display mild to moderate mental retardation or normal cognitive abilities and less severe epilepsy.

Surprisingly, the cortex of DCX knockout male mice is morphologically normal, with proper cortical lamination. A second gene mutated in lissencephaly is LIS1 which is also associated with microtubules since it interacts with dynein. Interestingly, Lis1 mutant mice also display a rather subtle phenotype in the neocortex but show prominent hippocampal defects, suggesting the involvement of compensatory genes [5,6,12–14]. Nevertheless, interneuron defects are present in both models and also in the human disorder. In contrast to the traditional knockout, acute inactivation of DCX using siRNA in mice cortex hampered cortical migration and produced a subcortical heterotopic placement [6]. These data further suggest that functional compensation occurs in DCX knockout mice.

Another gene mutated in a form of lissencephaly is Reelin [5,12]. Studies in *reeler* mice and biochemical studies show that Reelin, an extracellular molecule, is involved in a signaling pathway (involving Reelin, VLDLR, APOER2 and Disabled I) which most probably controls the final steps of cortical neuronal migration [12,15].

Cobblestone Lissencephaly

In cobblestone lissencephaly, the cortex lacks gyri and sulci and has a bumpy or cobblestone appearance. This type of malformation is thought to result from a defect in the limiting glial membrane that fails to transduce a stop signal, resulting in migratory neurons that have passed through the pia into the meninges inducing a mushroom like appearance of the cortex. Also in the brain midline, neurons appear to migrate through both pial membranes and cross the midline into the opposite hemisphere. These disorders include muscle-eye-brain disorder, Walker-Walburg syndrome and Fukuyama congenital muscular dystrophy that are characterized by muscular dystrophy, eye abnormalities. Particularly glycosyltransferases are mutated in these disorders [5,6,8].

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Cortical Frontal Eye Fields

Definition

►Frontal Eye Fields

►Supplementary Eye Field

Corticobasal Degeneration

Definition

Corticobasal degeneration involves several neuropsychological impairments, such as limb ►ataxia, visuospatial problems, acalculia (inability to perform mathematical operations), and ►aphasia.

►Ataxia
►Aphasia

Corticobulbar Tract

Definition

Fibers coursing from cerebral cortex to brainstem (also called bulb).

►Pathways

Corticofugal

Definition

Referring to a neural pathway that originates within the cerebral cortex and project to other parts of the central nervous system (CNS), including other regions of the cortex.

Corticonuclear Fibers

Synonyms

►Fibrae corticonucleares

Definition

On reaching the vicinity of their target region, the fibers of the pyramidal tract disengage themselves from the tract and form individual fibers, which are called corticonuclear fibers.

►Pathways

Corticonuclear Tract

Synonyms

Fibrae corticonucleares; Corticonuclear fibers

►Corticonuclear Fibers
►Pathways

Corticospinal Neurons

Definition

Neurons that have a cell body in layer V of the cerebral cortex and an axon that projects to the spinal cord. Most corticospinal neurons are found in motor areas of the frontal lobe and are involved in movement execution.

However, many corticospinal neurons are also found in somatosensory cortex and are involved in regulating the ascending flow of somatosensory information.

►Motor Cortex: Output Properties and Organization

Corticospinal Tract

Synonyms

Tractus corticospinal

►Pyramidal Tract
►Pathways

Corticospinal Tract Lesions

Definition

Lesions limited to the ►pyramidal tract produce a ►Babinski sign and ►paresis (i.e., negative symptoms

such as temporary weakness and loss of dexterity), but neither spastic ►dystonia nor permanent weakness.

►Babinski Reflex

Corticosterone

Definition

Major steroid hormone in rodents released from the adrenal cortex.

Cortico-Subcortical Re-Entrant Circuit

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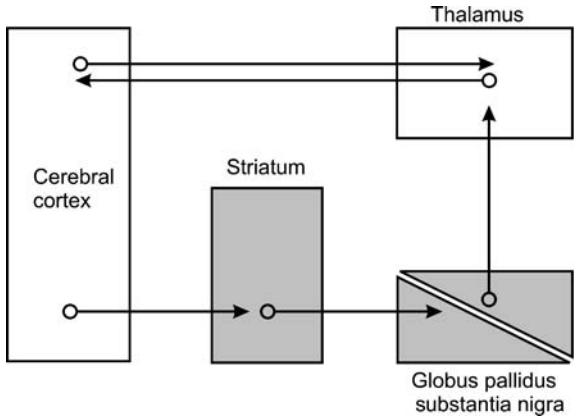
Synonyms

Basal ganglia-thalamocortical circuit; Cortical-basal ganglia circuit; Basal ganglia-thalamocortical loop

Definition

Cortico-subcortical re-entrant circuits are composed of a series of connections that start in a particular part of the cerebral cortex and lead via subsequent steps in the basal ganglia and the thalamus back to the same part of the cortex. More in particular, cytoarchitectonically and functionally distinct cortical areas in the frontal lobe form the focal point of these circuits. Each frontal cortical area projects to a specific region of the striatum and that striatal region projects via the globus pallidus or substantia nigra to a particular thalamic nucleus or part thereof. This part of the thalamus, in turn, is in reciprocal connection with the original frontal cortical area, closing the circuit (Fig. 1).

These cortico-subcortical re-entrant circuits are also being indicated as the basal ganglia-thalamocortical circuits. Three "families" of cortico-subcortical re-entrant circuits have been described: sensory-motor, complex or cognitive and limbic or emotional-motivational circuits. The recognition of this circuitous arrangement between the cerebral cortex, basal ganglia and thalamus has had great impact on our understanding of the neuronal substrate of forebrain functions and the pathophysiological basis of various neurological and psychiatric disorders.



Cortico-Subcortical Re-Entrant Circuit.
Figure 1 Basic diagram of the architecture of cortico-subcortical re-entrant circuits that involve the different areas of the frontal cortex, the basal ganglia (gray boxes) and the thalamus.

Characteristics

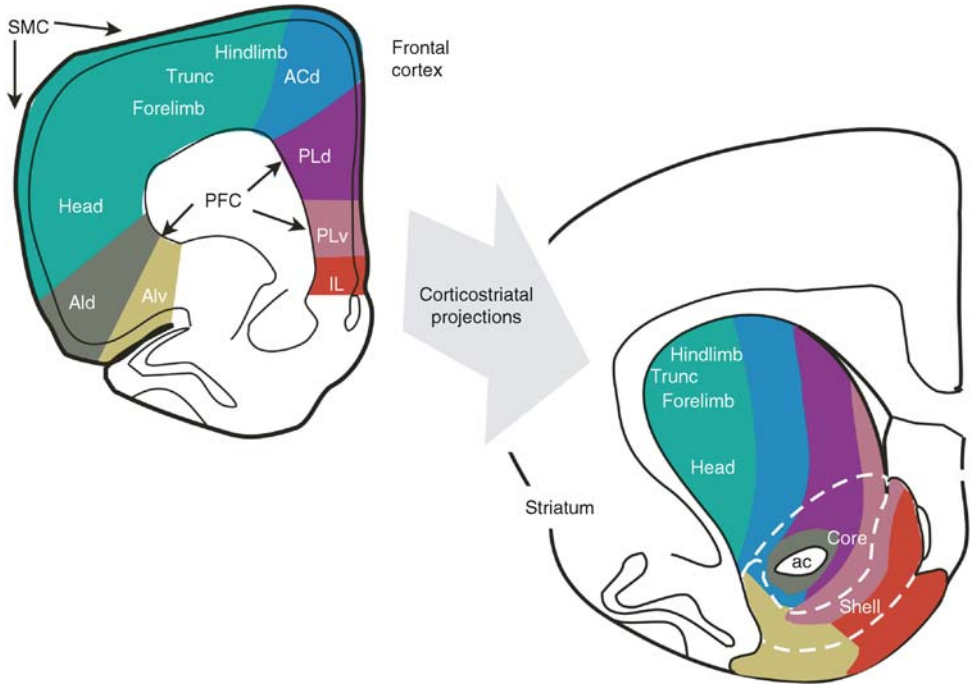
The connectional relationships between the cerebral cortex and the basal ganglia have been viewed in various ways in the past. Whereas initially it was thought that the basal ganglia send their output directly to lower brain structures such as the brainstem and spinal cord, Nauta and Mehler [1] showed that the basal ganglia mainly project to the thalamus. As a consequence, the influence of the basal ganglia reaches the cerebral cortex since the thalamus is reciprocally connected with the cortex. However, at that time the prevailing idea was that the basal ganglia, which themselves receive inputs from the cortex of the entire hemisphere, by subsequent steps of convergence, mainly direct their influence via the ventral anterior thalamic nucleus to the premotor cortex. In other words, the basal ganglia were considered to collect and integrate information from all functionally different cortical areas and direct their output via the thalamus to motor-related cortical areas, the basal ganglia in essence having an influence on the motor system. A major breakthrough was established with the landmark paper by Alexander and colleagues [2] who, on the basis of a reinterpretation of already existing neuroanatomical and electrophysiological data, proposed that the connections between the cerebral cortex, basal ganglia and thalamus are arranged in parallel, functionally segregated basal ganglia-thalamocortical loops or circuits. It became then generally accepted that, next to the premotor cortex, also extensive parts of the prefrontal cortex are under the influence of the basal ganglia and form part of cortico-subcortical re-entrant circuits. As a consequence, premotor and prefrontal cortices together with connectionally related parts of the basal ganglia and thalamus form a series of parallel,

partially closed circuits that subserve a wide range of motor, behavioral en emotional-motivational functions.

Architecture of the Cortico-Subcortical Re-Entrant Circuits

The more detailed architecture of cortico-subcortical re-entrant circuits is as follows. Architectonically and functionally distinct frontal cortical areas form the starting and re-entrant point of the basal ganglia-thalamocortical circuits [2,3]. The projections from the cerebral cortex to the striatum are highly topographically organized. Motor and premotor, including oculomotor cortical areas project to the dorsal and lateral parts of the caudate nucleus and putamen. Dorsolateral prefrontal cortical areas, involved in executive functions and working memory, project to intermediate, more ventrally located regions of the caudate-putamen complex. Finally, medial and orbital prefrontal areas, involved in emotional and motivational processes, project to the most ventral and medial parts of the striatum, including the ►nucleus accumbens (Fig. 2).

This corticostriatal topography forms the basis for three "families" of cortical basal ganglia-thalamocortical circuits, each consisting of several sub-circuits, that subserve sensory-motor, complex or cognitive and emotional-motivational behavioral functions. Next to these cortical inputs from the frontal lobe, the striatum receives projections from other cerebral cortical areas in more caudal parts of the hemisphere (parietal, occipital and temporal lobes), limbic structures, such as the amygdala and hippocampus, midline and intralaminar thalamic nuclei and the dopaminergic and serotonergic system. The striatum has therefore been designated as the input structure of the basal ganglia. Via different routes, the functionally different striatal regions reach distinct parts of the internal segment of the globus pallidus, the reticular part of the substantia nigra or the ventral pallidum that together form the output structures of the basal ganglia. These structures, in parallel, project to different thalamic nuclei that are in reciprocal contact with the original frontal cortical areas. Thus, the internal segment of the globus via specific parts of the



Cortico-Subcortical Re-Entrant Circuit. Figure 2 Schematic representation of the organization of the corticostriatal projections in rats. At the left hand side different motor and prefrontal cortical regions in the frontal lobe are represented in different colors. The projections to the striatum at the right hand side are highly topographically organized providing for functionally different sectors in the striatum related to different cortical areas represented in the same color. Even though there is a distinct topography in the corticostriatal projections, there also exists overlap between the different projection areas. Abbreviations of the various prefrontal cortical areas in the rat: *ACd*, dorsal anterior cingulate area; *AId*, dorsal agranular insular area; *AIv*, ventral agranular insular area, *IL*, infralimbic area; *PLd*, dorsal prelimbic area; *PLv*, ventral prelimbic area. Core and shell are distinct subregions of the nucleus accumbens in the ventral striatum.

ventral lateral and ventral anterior thalamic nuclei projects back to the premotor cortex, closing the so-called motor loop. The reticular part of the substantia nigra projects via specific parts of the ventral anterior and mediodorsal thalamic nuclei back to dorsolateral prefrontal areas, closing the so-called complex or cognitive loop. Finally, the ventral pallidum projects primarily to the mediodorsal thalamic nucleus which is connected to the medial and orbital prefrontal areas, closing the so-called limbic loop.

In the previous paragraph the basic architecture of the closed cortico-subcortical re-entrant circuits has been depicted. There are at least three aspects that are of interest in the context of our understanding of the structural and functional significance of these circuits.

First, the input and output structures of the basal ganglia are interconnected via two routes that have opposing effects on the basal ganglia output. The above-described striatal projections to the internal segment of the globus pallidus, the reticular part of the substantia nigra and the ventral pallidum from part of the so-called direct striatopallidal output pathway. The second, so-called indirect striatopallidal output pathway leads via subsequent synaptic interruptions in the external segment of the globus pallidus and the subthalamic nucleus to the basal ganglia output structures [3,4]. Stimulation of the direct pathway at the level of the striatum leads to a higher activity, stimulation of the indirect pathway to a lower activity at the level of the thalamocortical projections within a particular circuit. Interestingly, the direct and indirect striatal output pathways are modulated by dopamine D1 and D2 receptors, respectively. The direct pathway has been shown to facilitate, the indirect pathway to inhibit the expression of motor, cognitive and emotional behavioral output [4]. For normal functioning, a balance between the two output pathways is thought to be essential. Striatal dopamine levels have a strong influence on this balance, low levels leading to paucity and high levels to an excess of simple movements or complex behavioral output. The just described organization of the connections within a particular basal ganglia-thalamocortical circuit forms the neuronal basis for what is considered the basic function of the basal ganglia in relation to the cerebral cortex, i.e. the selection of an appropriate motor, cognitive or emotional behavioral output in a particular context [5].

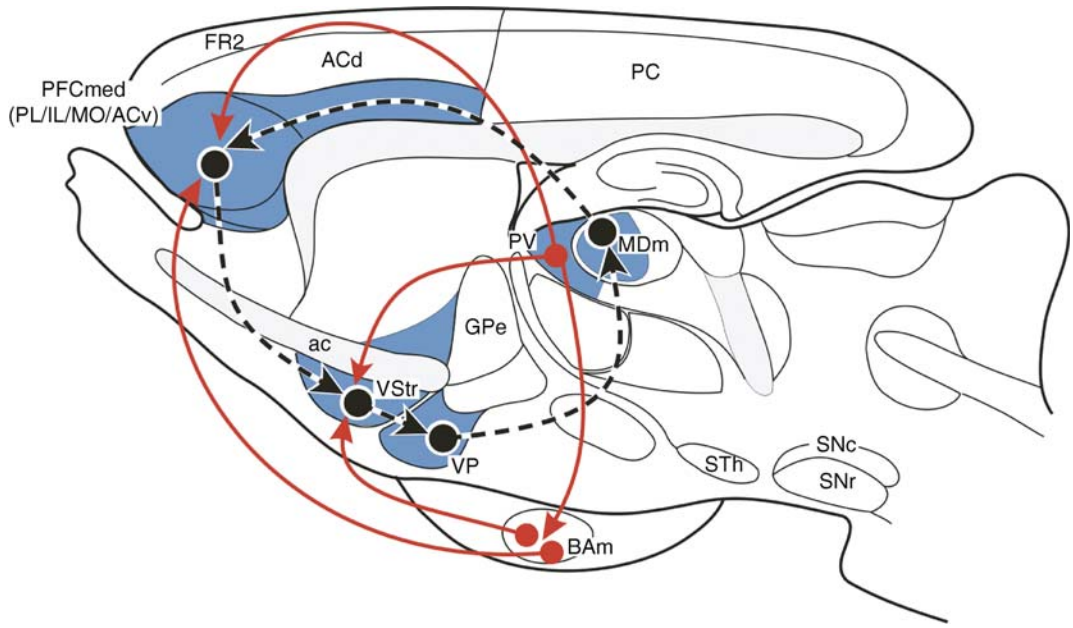
Second, it is very likely that the contextual information necessary for such selection mechanisms that take place within the basal ganglia-thalamocortical circuits enters these circuits at the level of the striatum. Various cortical areas in the parietal, occipital and temporal lobes project in a topographical way to the striatum where they converge with functionally and connectionally related corticostriatal projections from the frontal lobe. For example, the ventral and medial parts of the striatum that form the limbic loop starting in the medial and orbital prefrontal areas receive information from the hippocampus and amygdala. These two limbic structures feed information about the mnemonic and emotional aspects of the context in which a behavioral program must be selected. Interestingly, the hippocampus and amygdala not only project to the striatum, but also to the prefrontal cortical area that is the origin of the corticostriatal projections to the same part of the striatum. Similar arrangements exist for the projections of the midline and intralaminar thalamic nuclei to different parts of the striatum and frontal cortical areas (Fig. 3).

The midline and intralaminar receive primarily inputs from brainstem nuclei and are likely to determine the level of activity of individual basal ganglia-thalamocortical circuits [6]. The specific arrangements of cortical, limbic and thalamic inputs into basal ganglia-thalamocortical loops suggests that these circuits form part of larger distributed circuits that are involved in particular motor and behavioral functions.

Third, whereas the closed nature of the cortico-subcortical circuits has been emphasized, it is clear that there exist connections between these circuits that provide ways by which limbic and cognitive circuits might ultimately influence motor circuits. Indeed an ascending spiral of connections from limbic to motor circuits has been suggested on the basis striato-pallido-thalamic projections that shift from one loop to the other [7]. Likewise an ascending spiral from limbic via cognitive to motor loops has been described through the dopaminergic system [8]. Such arrangements of interconnections between circuits might form the basis for the gradual shift from unconditioned behaviors to conditioned behaviors to, finally, habit formation in the course of a behavioral learning process.

Clinical Relevance

The recognition of the cortico-subcortical re-entrant circuits and the realization that these circuits subserve the wide range of sensory-motor to cognitive and emotional-motivational functions has had great impact on the interpretation and understanding of the pathophysiological basis of several neurological and psychiatric diseases [9,10]. Thus, disturbances of way stations of the dorsally located motor circuit lead to classical neurological symptoms [9]. An example is Parkinson's disease in which the clinical signs of bradykinesia, rigidity and tremor are associated with a degeneration of the dopaminergic innervation of the dorsolateral, sensory-motor related part of the striatum (mainly putamen). Disturbances in cortical and basal ganglia way stations of the cognitive or complex loop (centered on the dorsolateral prefrontal cortex) are associated with executive function deficits (e.g. schizophrenia). Finally, disturbances of one or more way stations in the limbic cortico-subcortical re-entrant circuit has been



Cortico-Subcortical Re-Entrant Circuit. Figure 3 Schematic representation in a midsagittal view of the rat brain of a cortical-subcortical re-entrant loop (black, stippled arrows) involving the prefrontal cortex, the mediodorsal thalamus and the ventral parts of the basal ganglia. In addition, the relationship of the projections of the midline thalamic nuclei and the amygdala with this loop are represented in this scheme (red arrows). The organization is as follows. Distinct basal amygdaloid subnuclei project to restricted parts of the prefrontal cortex and the ventral striatum that are both part of the same cortical-subcortical re-entrant loop. Likewise, distinct nuclei of the midline and intralaminar thalamic complex project to prefrontal cortical and ventral striatal areas that in turn are interconnected. In addition, the midline nuclei project to that part of the basal amygdala that is related to the same loop. This scheme represents a cortical-subcortical circuit that involves the medial prefrontal cortex, the ventral striatum and the medial segment of the mediodorsal thalamic nucleus. Similar arrangements exist for the relationships of midline/intralaminar thalamic nuclei and basal amygdaloid nuclei with other cortical-subcortical re-entrant circuits. Abbreviations: *ac*, anterior commissure; *ACv*, ventral anterior cingulate area; *BAm*, basal amygdaloid nucleus; *FR2*, frontal area 2; *GPe*, external segment of the globus pallidus; *MDm*, medial segment of the mediodorsal thalamic nucleus; *MO*, medial orbital area; *IL*, infralimbic area; *PFCmed*, medial prefrontal cortex; *PC*, posterior cingulate area; *PL*, prelimbic area; *PV*, paraventricular thalamic nucleus; *SNc*, substantia nigra pars compacta; *SNr*, substantia nigra pars reticulata; *STh*, subthalamic nucleus; VP, ventral pallidum; VStr, ventral striatum; Core and shell are distinct subregions of the nucleus accumbens in the ventral striatum.

associated with various other psychiatric disorders such as substance abuse, obsessive-compulsive disorder or mood disturbances like apathy.

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Corticotropes

Definition

Cells in the anterior pituitary gland that secrete the stress hormone, adrenocorticotropin.

►Influence of Ca^{2+} Homeostasis on Neurosecretion

Cortisol

Definition

Major steroid hormone in humans released from the adrenal cortex.

Cost Function

Definition

The expression to be optimized in some objective function. The cost can correspond to some quantity we wish to minimize (e.g., energy, time) or maximize (e.g. smoothness), or to the degree to which the performance deviates from a mathematically defined criterion. Following the imposed constraints (e.g. at the beginning and end-points of a movement), minimizing the cost function with respect to its arguments enables us to predict the optimal performance in the desired context.

►Arm Trajectory Formation
►Neural Networks for Control

Co-transmission

Definition

Co-transmission refers to the release of more than one neurotransmitter from a single neuron. Co-transmitters may be released together or independently depending on their subcellular storage and the level of activation of the neuron. Often peptides are co-released with small molecules. The co-transmitters may have different release properties and can exert different effects on target neurons.

Co-transporter

Definition

Co-tranporter (also called symporter) is a transmembrane protein that uses the energetically favorable transport of an ion down its electrochemical gradient to drive the uphill transport of other ion species in the same direction.

►Ion Transport

Cough

►Respiratory Reflexes

Coughing (Fishes)

►Odor-Sampling Behavior

Coupling Coefficient

Definition

The coupling coefficient is a measure of synaptic strength of an electrical synapse. It equals the ratio of the postsynaptic voltage response over the presynaptic voltage stimulus of two electrically coupled cells.

Because of the low-pass frequency filter characteristics of an electrical synapse, its coupling coefficient depends on the frequency characteristics of the stimulus. The steady-state coupling coefficient for direct current (DC) stimuli (i.e., stimulus frequency = 0) is a function of the electrical resistance of the gap junction and the input resistance of the postsynaptic cell. The non-steady state solution of the coupling coefficient for alternating current (AC) stimuli (i.e., stimulus frequency $\neq$ 0) includes capacitance terms represented by the membrane capacitance of the postsynaptic cell.

►Electrical Synapses

Courtship

Definition
The behavior of a male courting a female to seek sexual interaction.

Covalent Regulation

Definition
Control of enzyme activity by covalent bonding of phosphate group to sites other than the active site of the enzyme.

Covert Shift of Attention

Definition
In contrast to overt shifts of attention, in which the eyes or body is directed towards a new focus of attention, covert shifts of attention cannot be directly observed from a second person. Attention is directed from one location to another without overt behavior. Neural systems involved in covert and overt attentional shifts show strong overlap. Brain areas controlling covert shifts of attention include the posterior parietal cortex and frontal eye fields.

►Attention
►Frontal Eye Fields

CPG

Definition
►Central Pattern Generator

CpG Dinucleotide

Definition
The most common site of DNA methylation in adult somatic tissues.

CpG Island

Definition
CpG islands are regions of genomic DNA enriched for CG dinucleotides located in 35–50% of gene promoters.

Cramps

Definition
Cramps are spontaneous, paroxysmal, prolonged and painful contraction of one or more muscles.

Cranial Nerves

Synonyms
Nn. Craniales

Definition
The cranial nerves are those nerves originating in the brainstem (midbrain, pons, and medulla) with the exception of the first and second cranial nerves, which are not true peripheral nerves but rather are fiber tracts of the brain. The 12 cranial nerves can be divided into sensory, motor or mixed nerves. Cranial nerves VII and IX carry parasympathetic innervation to the salivary glands.

- Olfactory nerve (I)
- Optic nerve (II)
- Oculomotor nerve (III)
- Trochlear nerve (IV)
- Trigeminal nerve (V)
- Abducens nerve (VI)
- Facial nerve (VII)
- Vestibulocochlear nerve (VIII)
- Glossopharyngeal nerve (IX)
- Vagus nerve (X)
- Accessory nerve (XI)
- Hypoglossal nerve (XII)

CREB

Definition
CREB is an activator that recognizes the consensus CRE site. It is also found at additional DNA sequences

(AP1 and GRE sites) in a complex containing other activators. The transcriptional activity of CREB is dynamically regulated by phosphorylation. The most well studied phosphorylation site is serine 133. Other phosphorylation events can repress its activity. CREB can be bound regardless of its phosphorylation state, however, for some genes CREB is only recruited to their CRE sites upon phosphorylation. CREB binds as a homodimer or heterodimer. Heterodimerization confers repressive activity of CREB as part of a larger complex of repressor proteins.

►Promoter

Creep

Definition

The phenomenon of increasing strain in time under constant stress.

►Mechanics

c-Rel (REL)

►Nf-κB – Potential Role in Adult Neural Stem Cells

Cresyl Violet Staining

Definition

It is a common method of neuronal tissue staining. Crest violet, a basic dye, binds to the acidic component of cytoplasm, the RNA-rich ribosomes, nuclei and nucleoli, staining the cell bodies.

Cretaceous

Definition

The period approximately between 130 and 70 million years ago.

►Evolution of the Brain: At the Reptile-Bird Transition

Creutzfeldt-Jakob Disease (CJD)

Definition

Most common human subacute ►transmissible spongiform encephalopathy (►prion disease), and appears in several variants: sporadic, inherited or acquired (e.g., iatrogenic), the latter being due to the same agent responsible for Bovine Spongiform Encephalopathy in cattle (BSE or "mad cow disease"). Patients may initially present with non-specific symptoms, such as withdrawal, forgetfulness, asthenia and insomnia, with impairment of multiple neurological systems (visual, ►pyramidal, ►cerebellar and neurocognitive systems), spontaneous ►myoclonic jerks and occasionally ►progressive supranuclear palsy. The condition progresses to a totally dependent state within 10 to 12 months. Histological features include spongioform degeneration, neuronal cell loss and astrocytosis.

Crimp

Definition

Wave like pattern of the collagen fibrils in the superficial zone of articular cartilage.

►Articular Cartilage

Cristae

Definition

Sensory tissue of the semicircular canals. The three semicircular canals have swellings, called ampullae and within each ampulla is the sense organ, called the crista. In the cristae the hairs of the hair cells are embedded in a gelatinous mass, called the cupula, which extends across the ampulla.

►Semicircular Canals
►Vestibulospinal Responses

Critical Period

Definition

1. The time during which an organism acquires normal function if it is exposed to normal conditions (see also sensitive period).

2. A postnatal period in which experience induces a significant modulation of brain function and rearrangement of neural circuitry.

Cross-adaptation in Sensory Systems

Definition

Adaptation is the phenomenon whereby sustained or repeated exposure to a sensory stimulus results in a reduction in the sensory response. For a cell in a sensory system that responds to more than one stimulus, cross-adaptation refers to the effect of adaptation to one stimulus on the sensory responses to the other stimuli to which the cell responds.

Cross-associative Memory

Definition

Same as hetero-associative memory.

►Associative Memory

Crossbridge

A crossbridge refers the binding of the contractile proteins myosin and actin to form actomyosin. The formation of crossbridges during a muscle contraction is essential to the generation of force and movement.

Cross-bridge Theory

Definition

The cross-bridge theory of muscle contraction states how force is produced, and how the filaments actin and myosin are moved relative to each other to produce muscle shortening. In the cross-bridge theory, side-pieces that are fixed in a regular pattern on the myosin filament (cross-bridges) are thought to undergo cyclic attachment and detachment to specific binding sites on the actin filament. During an attachment/detachment cycle, the cross-bridge head is thought to undergo a rotation and so pull the actin filament relative to the myosin. Each of these cycles is associated with a relative movement of □10 nm and a force of about 2–10 pN. Furthermore, one cross-bridge cycle is thought to occur with the energy gained from the hydrolysis of one adenosine triphosphate (ATP). The cross-bridge theory was first formulated in a quantitative manner by Andrew Huxley in 1957. It has since undergone many changes and adaptations, but the basic principles put forward at that time still remain accepted in the scientific community today.

►Force Depression/Enhancement in Skeletal Muscles

Cross-covariance

Definition

A linear measure of the relationship between two variables. The cross-covariance is computed as the average of the products of the deviations of each variable from their respective mean.

►Signals and Systems

Cross-generalization

Definition

In sensory psychophysics this refers to generalization of a behavioral response from the stimulus on which an animal is trained to another stimulus. It is used to test similarities between stimuli.

Cross-modal

Definition

From two or more different sensory modalities. Used to refer to: (a) combinations of stimuli from different sensory modalities (e.g., a combination of light and sound) that normally evoke different subjective experiences, (b) the spatial register among the different receptive fields of a multisensory neuron, and (c) the spatial register among different sensory maps. Also

used to refer to tasks involving matching and/or transfer of information among modalities.

►Multimodal Integration

Cross-modal Extinction

Definition

A disorder that typically follows damage to the right hemisphere, in which patients are able to detect single tactile stimuli applied to the contralesional hand in isolation, but show impairments in detecting the same tactile stimuli when an additional visual stimulus is presented on the ipsilesional side.

►Multimodal Integration

Crossmodal Integration

►Multimodal Integration

Cross-modal Plasticity

Definition

The neuroanatomical, neurophysiological, perceptual, and/or behavioral changes that may occur in one or more sensory modalities following damage to, or selective impairments in, another sensory modality.

For example, changes in auditory or tactile processing as a result of temporary or permanent blindness may be a result of crossmodal plasticity.

►Multimodal Integration

Cross-modality Matching

Definition

A psychophysical method that requires adjustment of the perceived strength of one sort of stimulus (e.g., light intensity) so that its matches that of another sort of stimulus (e.g., sound intensity).

►Psychophysics

Crossopterygian

Definition

The coelacanth fish *Latimeria chalumnae*, a deep-sea fish of ancient lineage discovered in the ocean waters off the South African coast in the 1930s.

►Evolution of Brain: at Invertebrate–vertebrate Transition

Cross-reactivity

Definition

Antibody or T cell receptor interaction with more than one antigen. Cross-reactive lymphocytes are often activated by a foreign antigen that has similarities to another antigen, usually a self antigen.

►Anti-DNA Antibodies against Microbial and Non-Nucleic Acid Self-Antigens

Cross-spectrum

Definition

The linear relationship between two variables, expressed in the frequency domain.

►Signals and Systems

Crotalidae

Definition

A family of venomous snakes, comprising rattlesnakes, mokasen snake, bushmaster, etc. In some taxonomy it is a sub-family (Crotalinae) of Viperidae.

►Evolution of the Brain: At the Reptile-Bird Transition

Cryophilic

Definition
A preference for colder temperatures.

Cryptochrome

Definition
A family of proteins that form integral components of the core circadian clock machinery and/or the regulatory pathways for light entrainment of the molecular circadian clock in animals and plants. Cryptochromes are receptors for blue and ultraviolet light, which share structural similarity and evolutionary origin with DNA photolyases. In the Drosophila circadian clock, CRYPTOCHROME functions primarily in light entrainment; light stimulates interactions between CRYPTOCHROME and TIMELESS, which promotes degradation of TIMELESS and suppresses function of PERIOD-TIMELESS heterodimers to cause resetting of the circadian clock. In mammals, cryptochrome is an essential component of the negative arm of the circadian feedback loop. Plant cryptochromes also regulate response of the circadian clock to light.

Abbreviation: Cry.

►Clock

Cryptochrome

Definition
Class of potentially blue-light sensitive proteins related to the bacterial photolyases, which contain two chromophores (pterin and flavin). In mammals, they constitute together with the Period proteins the major repressive function during the dark phase.

►Clock-Controlled Genes

CSP

Definition
Cystein string proteins. Highly conserved synaptic vesicle proteins characterized by a central string of cysteine residues (with multiple palmitoylations) and an N-terminal J-domain indicative of chaperone functions (e.g. facilitating folding or conformational changes of other critical proteins). Known to interact with voltage-gate Ca^{2+} channels.

►Synaptic Proteins and Regulated Exocytosis

C-start Escape

Definition
An escape response observed in many fishes and larval amphibians in response to sudden aversive stimuli. It consists of two phases: an initial tight bend away from the direction of the startling stimulus, causing a C-shaped curve in the body when observed from above. This C-shaped bend is followed by a rapid acceleration away from the animal's starting position. The C-start escape is typically initiated by a pair of large brainstem neurons, called Mauthner cells.

►Auditory-Motor Interactions
► Mauthner Cell

CT

►Muscle Imaging Techniques: Computerized Tomography

CT Afferents

►Tactile C Fibers

CT Fibers

►Tactile C Fibers

CTA

►Conditioned Taste Aversion

Culmen

Definition

Part of the vermis cerebelli lying above the primary fissure. Belongs to the anterior lobe. Like the entire vermis cerebelli, the culmen receives its afferents primarily from the spinal cord. Hence it is part of the so-called spinocerebellum = palaeocerebellum.

►Cerebellum

Culture of Neurons

Definition

Experimental preparation consisting of a layer of neuron cells, grown on a physical substrate which also contains electrodes for recording and stimulation. Cultures may be made from dissociated neurons, usually from cortical areas, thus resulting in a monolayer of cells which develop strong, random, mostly excitatory connections; or they may come from slices of nervous tissue – organotypic cultures, thus maintaining the basic anatomical features of the tissue of origin. Cultures of dissociated neurons can be kept in healthy conditions for a long time (several months) and their morphological and physiological properties resemble those of the tissue of origin, but cannot be directly compared to in-vivo preparations. Widespread, synchronous bursting activity is their normal mode of spontaneous response, reflecting their lack of afferent connections.

Cuneate Fasciculus

Definition

The cuneate fasciculus is a large bundle of axons running just lateral to the gracile fasciculus. Together the cuneate and gracile fasciculi form the dorsal columns in the dorsal medial part of the spinal cord. The dorsal columns are formed by the axons of neurons in the dorsal root ganglia just outside the spinal cord and carry somatosensory information from the body to the caudal medulla. The cuneate fasciculus carries information from the arms and the upper trunk.

Cuneate Nucleus

Definition

The cuneate (Latin for wedge-shaped) nucleus is a nucleus in the caudal medulla that receives tactile, proprioceptive and vibratory input from the arm and upper trunk by way of the cuneate fasciculus. It is immediately lateral to the gracile (Latin for slender) nucleus (see below).

Cuneus

Definition

Part of the occipital lobe visible on the medial aspect of the hemisphere. Involved in the processing of visual information.

►Telencephalon

Cupula

Definition

A fluid-tight partition that lies above the crista and spans across the walls and roof of the ampulla in the semicircular canals. Cupula deflection by endolymph movement displaces the embedded stereocilia of the canal receptor cells.

►Semicircular Canals
►The Peripheral Vestibular Apparatus

Curvature Equation

Definition

A local measure of deviation from linearity of a curve. It is invariant under rotations and translations. Given a

planar curve in time (x(t), y(t)), parameterized such that the speed V(t) > 0, the curvature at every point along the curve is expressed as follows: where dot means derivative with respect to time. Curvature is measured in units of 1/cm and is dependent only on the path (regardless of the speed profile).

►Arm Trajectory Formation

Cushing's Syndrome

Definition

Endocrinological disorder characterized by consistently elevated levels of cortisol often resulting from tumors e.g., located in the pituitary (=Cushing's disease) or adrenal.

►Hypothalamo-Pituitary-Adrenal Axis, ►Stress and Depression

Cutaneomuscular Reflexes

Definition

Reflexes evoked by a variety of cutaneous, low and high threshold afferent fibers. Generally these are flexion reflexes; however, extension can occur when this pattern of muscle activation is required to remove the stimulated region of the skin from the stimulus, which is usually noxious.

Cutaneous Mechanoreceptors, Anatomical Characteristics

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Synonyms

Tactile (touch) receptors; Pressure receptors; Vibration receptors

Definition

Morphology of Sensory Receptors in the Skin for Light Mechanical Stimulation

Light mechanical stimulation causes tactile, pressure or vibration sensations but not painful sensations. Sensory receptors for such light mechanical stimulation applied to skin are called cutaneous mechanoreceptors, and are located in the epidermis, dermis, or sometimes at subcutaneous tissue. They are innervated by nerve fibers with large to medium caliber. Almost all mechanoreceptors except one are the primary sensory cells, the nerve terminals specially evolved for receiving mechanical energy, surrounded by lamellae or accessory cells, however, the rest (Merkel cell) are probably secondary sensory cells, originated from the neural crest, making synapse like contacts with nerve endings, although there have been controversial debates on the functional role in mechanosensory transduction.

Characteristics

Classification of Cutaneous Mechanoreceptors

Several mechanoreceptors can be differentiated in terms of the location in the skin and morphology. Included among them are Merkel cell-neurite complex, Ruffini endorgan, Meissner's corpuscle, hair follicle, and encapsulated corpuscles, such as, Krause ending, ►Pacinian corpuscle, and others. Merkel disk receptors (Glandry cells) and Herbest corpuscles, similar to Pacinian corpuscles, are found in lower animals such as birds. Anatomical characteristics of these receptors have been clarified electronmicroscopically, and they are now confirmed histochemically and immunochemically. Recent histochemical and immnochemical works are not referred to in this essay. The function of these receptors is found elsewhere in this Encyclopedia. Here, the detailed morphology is described.

Location of Cutaneous Mechanoreceptors

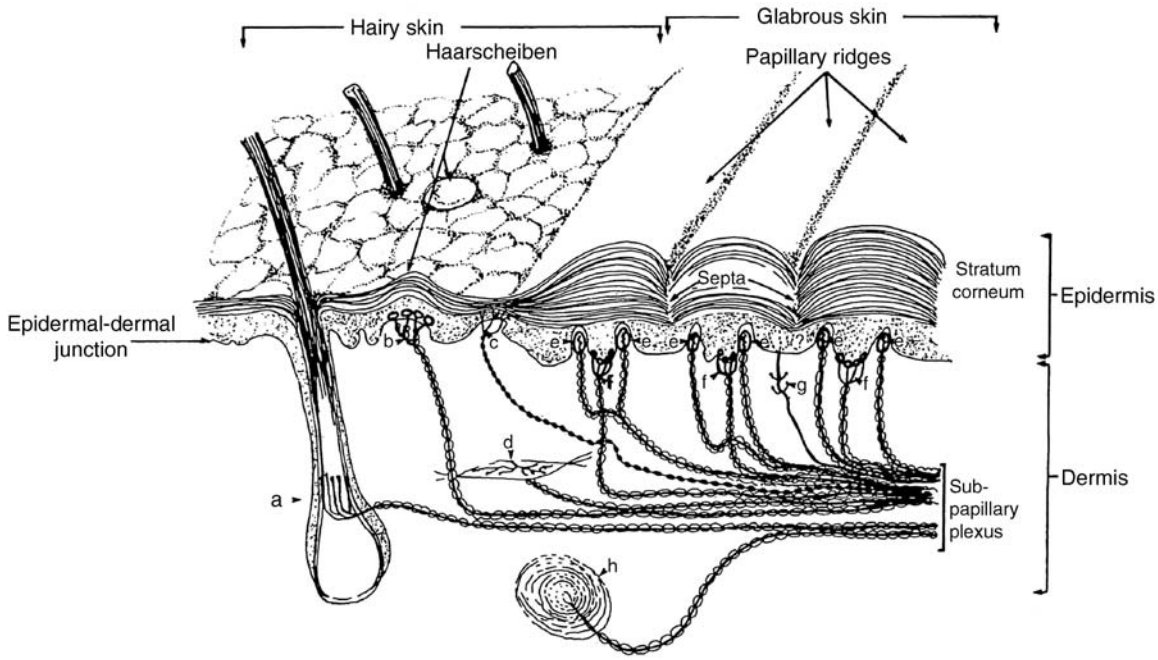
Different cutaneous mechanoreceptors are present between hairy and ►glabrous skin (Fig. 1).

In the hairy skin, Merkel cell-neurite complexes are seen at the base of touch dome, dome-like elevation of the skin, and hair follicles of guard and down hairs are also found in the dermis. In the glabrous skin, on the other hand, Merkel cell-neurite complexes locate at the rete of the papillary ridge and Meissner corpuscle (or Krause end bulb in cats) are found at the dermal papilla. In both skins, Ruffini endings are deep in the dermis and Pacinian corpuscles are in subcutaneous tissue. Merkel disk receptors and Herbest corpuscles are located at the dermis of some birds.

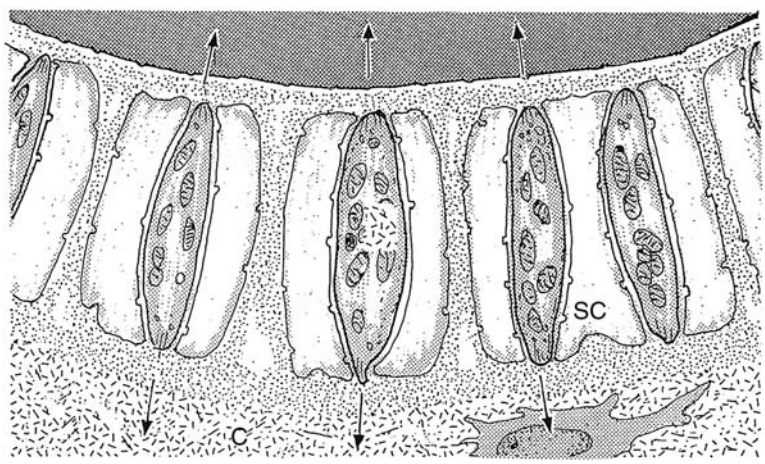
Detailed Definition

Hair Follicle Receptors (Lanceolate Receptors)

In guard hairs and down hairs, the nerve endings run in parallel to the hair shaft and give rise to the lanceolate terminals immediately below the sebaceous glands. In



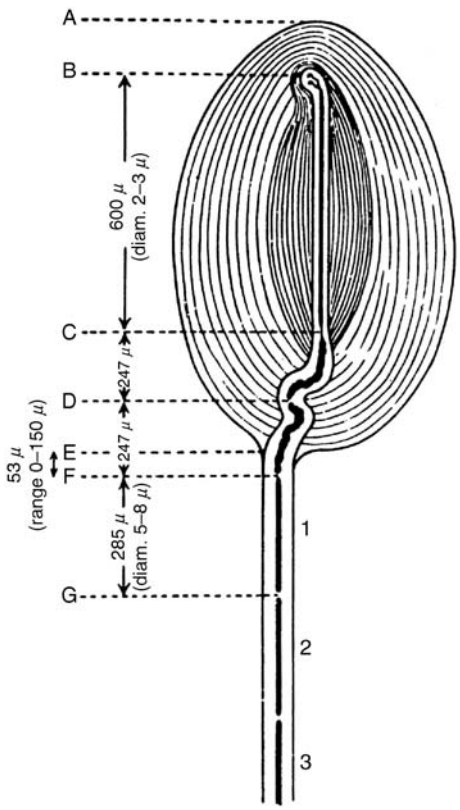
Cutaneous Mechanoreceptors, Anatomical Characteristics. Figure 1 Location of low threshold cutaneous mechanoreceptors with some free nerve endings at hairy skin (left half) and glabrous skin (right half) of primate. A, hair follicle with "palisade" ending; b, "Haarscheiben" or touch dome with Merkel cell-neurite complexes at base; c, free nerve ending; d, Ruffini endings; e, Meissner corpuscle in dermel papillae; g, free nerve ending; h, Pacinian corpuscle (Reproduced from AR Light and ER Perl 'Peripheral Sensory System', In: PJ Dyck et al. (eds) Peripheral Neuropathy, vol.1, WB Saunders Company. Philadelphia, 1984, pp. 210–230, Fig. 9–3).



Cutaneous Mechanoreceptors, Anatomical Characteristics. Figure 2 Schematic illustration of lanceolate endings in guard hair. C, cornium of hair follicle; SC, Schwann cell. (Reproduced from Andres and von During (1973) Handbook of sensory physiology, vol. 2 somatosensory system, (ed A Iggo), Springer, Berlin Hiedelberg New York, Fig. 7a.)

an electronmicroscopic picture, they are seen in a circumferential array or palisade (Fig. 2) [1].

The terminals are covered by swollen ►Schwann cells except for narrow slits at their inner and outer sides. In some nonsinus facial hair follicles, Ruffini-like spray terminations encircling the hair follicle just below the sebaceous gland have been reported and the term "pilo-Ruffini complex" is proposed [2].



Cutaneous Mechanoreceptors, Anatomical Characteristics. Figure 3 Schematic illustration of a lamellated corpuscle, representative of lamellated corpuscles. A single axon invades the lamellae to from a nerve ending. Two kinds of lamellae are identified; densely spaced lamellae, inner core, and loosely spaced ones, outer lamella. (Reproduced and modified from TA Quillian and M Sato (1955) The Distribution of Myelin on Nerve Fibres from Pacinian Corpuscles, J. Physiol. 129: 167–176, Fig. 8).

Krause Endings

Two forms of small lamellated ►end bulbs were described by Krause (1880); the cylindrical form in non-primates, e.g., cats, and the globular or spherical form in man and monkeys. *Cylindrical end bulb of Krause* is present in the dermis, often very close to the epidermis but not usually in the dermal papillae or the glabrous skin in non-primates [3]. The cross section reveals the small-sized lamellated corpuscle (Fig. 3); that is the inner core consists of less than 10–30 sheets of Schwann cell lamellae which surround a nerve terminal and is separated from the capsule by a small capsular space.

There are morphological variations from simple unbranched terminals seen in the majority (51%) to branched [2]. The length ranges from 30 to 125 μm and the mean diameter is 12.5 (ranging from 5 to 40) μm [3].

Spherical end bulb of Krause is, on the other hand, present at the mucous membrane such as oral mucosa, conjunctiva and genitalia. Their presence in glabrous skin of human extremities is also reported. So-called genital corpuscles in both primates and non-primates have morphological features similar to those of Krause's spherical end bulb. The typical end bulb is oval or spherical with a mean diameter of 100 μm. It has a capsule made of two to six layers which surround the inner core without a distinct capsular space. In the inner core, nerve terminals covered with Schwann cell lamellae run in a tortuous manner [2].

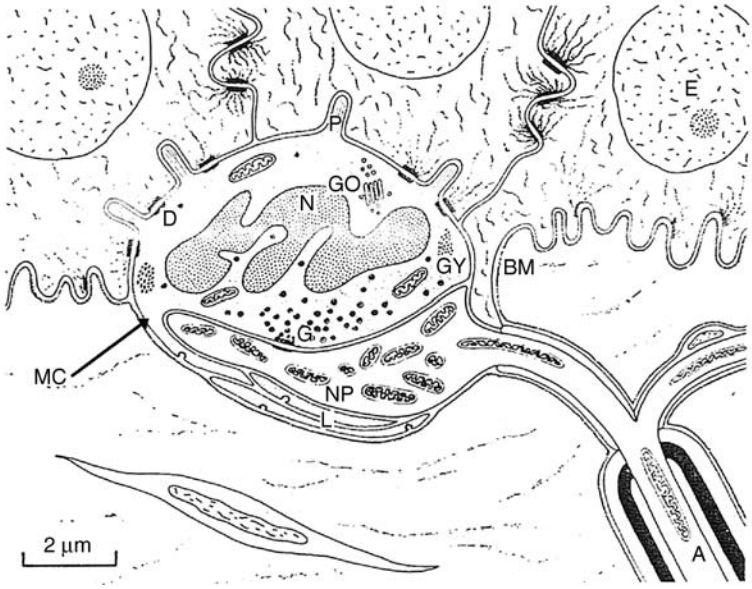
Meissner Corpuscles

These were originally described by Wagner and Meissner (1872). They are incompletely encapsulated corpuscles, occupying the dermal papilla in the glabrous skin [2]. The size is relatively large, 150 μm long and 40–70 μm in diameter. The capsule comprises of dispersed perineural lamellae and thick collagen fibers mainly encasing the basal side, but the capsular space is ill-defined. The inner core appears horizontally layered. It is composed of Schwann cells and nerve terminals, and these two components are arranged horizontally and alternatively layer by layer and lamellae of Schwann cells sandwich the oval or ellipsoidal nerve terminals. ►Tonofibrils are followed from the epidermal keratinocytes to collagen fibers in the dermis and some of them enter the upper part of the capsule and others are continuous with the endoneural sheath of the basal half of the capsule [4]. Several myelinated ►axons enter the capsule.

Merkel Cells

Merkel cells have been found in the skin of mammals and amphibians since Merkel (1875). When Merkel cells are associated with a neurite, the complex is often called a *Merkel cells-neurite complex* or rarely as a touch corpuscle. Merkel cells are characterized with a lobulated nucleus and distinct vesicles. In mammals, they are found in the epidermis of both glabrous and hairy skin (Fig. 4).

In hairy skin, they are situated at the bottom of the epidermis, in clusters of 50–70 cells, under the touch dome, a dome-like elevation, and is often associated with a guard hair called a Haarscheibe (hair disk). In the glabrous skin with ridging, Merkel cells are situated in a group in the rete of the epidermal ridge, including the bottom, through which the duct of the sebaceous gland passes. Merkel cells are 6.9 × 3.9 μm, and oriented so that the nuclei are horizontal, and make ►desmosomes with neighboring keratinocytes [5]. Cells have a number of cytoplasmic processes, ►microvilli (diameter, 0.14 μm, length, ca 1 μm; n = 26) [6] projecting into the invaginations of neighboring keratinocytes. A single myelinated nerve axon of a large



Cutaneous Mechanoreceptors, Anatomical Characteristics. Figure 4 Schematic illustration of Merkel cell neurite complex. Axon; BM, basement membrane; D, desmosome; E, epithelial keratinocyte nucleus; G, granulated vesicles; GO, Golgi apparatus; GY, glycogen; L, lamellae underlying the nerve plate; MC, Merkel cell; N, multilobulated nucleus; NP, nerve plate; P, cytoplasmic process. (Reproduced from Iggo and Muir (1968) J Physiol 200:763–796, Text Fig. 2.)

diameter innervates Merkel cells in the field of about 100 × 300 µm, and their terminals make expanded and fattened disks (about 7 µm in diameter and 1 µm thick). The nerve disks are located on the dermal side of the Merkel cells, making synapse-like contacts with the latter. Merkel cells contain clear and dense-cored vesicles, mitochondria and Golgi apparatus in the cytoplasm, and vesicles (125,000–200,000) [2] are gathered between the nucleus and cell membrane facing the nerve disk, and the latter also contains mitochondria.

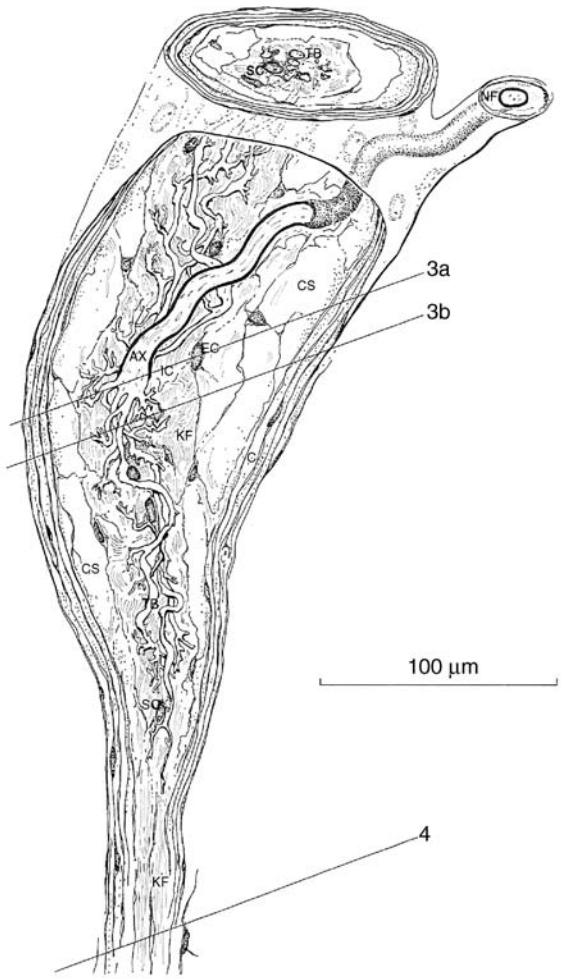
Merkel Disk Receptors

Merkel disk receptors are encapsulated and often called *Grandry corpuscles* after Grandry (1869) who first described the receptor. They have been found in the dermis in the bill and tongue of aquatic birds, but are absent from Japanese quail and the domestic hen. The receptor is spherical with a mean diameter of 30–80 µm and has a single-layered capsule. Two to seven Merkel cells (i.e., Grandry cells) or satellite cells (hemispherical, 50 × 15 µm in size) are present inside the capsule. The number of Merkel cells contained varies with different species [7]. The nerve terminal of a flattened disk form (40 µm in diameter × 20 µm in thickness in duck) is sandwiched between two Merkel cells [8]. Merkel cells in this receptor show three morphological features similar to that of Merkel cells in the mammalian Merkel cell-neurite complex, as follows; (i) there are numerous finger-like cytoplasmic protrusions on the hemispheric surface of the cell, the processes that interdigitate with Schwann satellite cells surrounding the cells. Merkel cells in this receptor have desmosome with Schwann cells but the desmosome is absent in the processes. (ii) The cytoplasm contains osmiophilic dense-cored vesicles (120–250 nm in diameter) scattered throughout the cytoplasm, although the vesicles are concentrated adjacent to the nerve endings in the mammalian Merkel cells. (iii) Junctional zones are formed between the Merkel cell and the nerve terminal. It is argued to classify satellite cells in this receptor as Merkel cells, although they are differentiated on the basis of whether they are located in the epidermis or dermis and whether they are encapsulated or not [2].

Pacinian Corpuscles

Lehman and Vater (1741) first described this corpuscle. The corpuscle is present deep in the subcutaneous tissue, at the interosseous membrane and at the mesentery in primates and non-primates. The perineural or outer lamella, made of 20–70 layers, forms a thick capsule and contains an inner core with many Schwann cells (inner lamella). An unmyelinated nerve terminal occupies the center of the inner core. The receptor is oval and rice-seed sized; the overall size ranges from 0.5 to 2 mm in length and is about 0.7 mm in diameter,

so large that it is visible when it presents at the mesentery or interosseous membrane. The lamellated structure looks like a section through an onion (Fig. 3). A single nerve fiber enters at one end of the corpuscle. After giving rise to a single Ranvier's node, it gets unmyelinated and travels to the other end of the corpuscle along the longitudinal in the inner core. The inner core lamella has a profile of semicircles with gaps between the half circles aligned so as to produce two clefts, with 180° apart, into which the unmyelinated nerve terminal with oval appearance at cross section projects the footlike extensions [9]. Nerve terminals are densely packed with a large number of mitochondria.



Cutaneous Mechanoreceptors, Anatomical Characteristics. Figure 5 Schematic illustration of Ruffini ending. AX, axon; cs, capsular space; KF, collagen fiber; IC, inner core; TB, terminal raminification of the axon. (Reproduced from Andres and von During (1973) Handbook of sensory physiology, vol. 2 somatosensory system, (ed. A Iggo), Springer Verlog, Berlin Hiedelberg New York, Fig. 5).

Ruffini Endings

These receptors were originally described by Ruffini (1983). Ruffini endings are spindle-shaped with the length ranging from 0.5 to 2 mm, and lie in the dermis both in the glabrous and hairy skin. A schematic illustration of the receptor is shown in Fig. 5.

The outer capsule of 3–5 lamella, originating from perineural cells, surrounds the fluid-filled space between the capsule and inner core, and the space is divided into several compartments. The inner core is filled with collagen fibers running continuously, and supplied by a large myelinated axon which breaks up to form a dense brush-work of fine branches and terminals [10]. A single axon innervates several endings.

Sinus Hair Follicles

Sinus hairs are present in the skin of mammals: they are vibrissae or whiskers in the face, carpal sinus hairs on the foreleg, tactile hairs or ▶tylotrich hairs in other parts of the body. They are characterized by their large diameter and the length of the hair, the presence of a vascular sinus in a large bulbous capsule, associated erectile muscles, and a rich innervation. Nerve terminals are present in the midregion of the follicle below the sebaceous gland. The four kinds of nerve terminals are noted in the facial sinus hairs [1]: (i) Merkel cells around the perimeter of the hair in the basal stratum adjacent to the glassy membrane, (ii) lanceolate nerve terminals lying in the inner hair follicle on the other side of the glassy membrane from the Merkel cells, (iii) small lamellate corpuscles, and (iv) fine nerve terminals. Carpal sinus hairs lack lanceolate nerve terminals but are associated with Pacinian corpuscles clustered around them. Tylotrich hairs have lanceolated nerve terminals but no Merkel cells, however, they are associated with Merkel cells in the epidermis to form hair disks.

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Cutaneous Mechanoreceptors, Functional Behavior

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Synonyms

Tactile afferents; Low-threshold cutaneous mechanoreceptors; Cutaneous receptors

Definition

The skin is the largest organ of the body and is richly supplied with specialized sensory endings of low mechanical threshold. These cutaneous mechanoreceptors allow us to feel the weak forces generated by a slight breeze and to differentiate between the textures and shapes of objects we touch and manipulate; they also contribute to ►proprioception. Yet the tactile system subserves not only the sense of "touch" in the broadest interpretation of the word, which implies that a stimulus can be felt; cutaneous mechanoreceptors are also important in fine motor control (particularly of the hand), which – depending on the task – may or may not require conscious attention. The remarkable versatility of the human hand depends not just on its anatomical structure but, in particular, on the sophisticated neural machinery that controls it. We use our hands to explore the physical world within our reach and, with tools, the world beyond our reach, and to act on the world through manipulation of environmental objects. To control both the exploratory and manipulatory functions of the hand, the brain must obtain accurate descriptions of various mechanical events that take place when objects are brought into contact with the hand, or when the fingers make contact with an object. Cutaneous mechanoreceptors in the fingers play crucial roles in providing such information. The glabrous (hairless) skin of the human hand contains approximately 17,000 low-threshold mechanoreceptors that provide us with our remarkable capacities to discriminate shape, texture and force [1]. This chapter deals only with the functional properties of human cutaneous mechanoreceptors, assessed via the technique of ►microneurography.

Characteristics

Quantitative Description

Glabrous Skin

Four types of specialized mechanoreceptor terminal can be identified histologically in human hairless (glabrous) skin – two located superficially and two deeper [1]. In the upper layers of skin there are groups of expanded disc-like endings that arise from branched axons and which are closely associated with specialized cells in the basal layer of the epidermis (Merkel cell-neurite complexes); within the intradermal papillae lay elipsoidal encapsulated endings (Meissner's corpuscles), the long axis of which is oriented normal to the skin. In the subpapillary dermis one finds the encapsulated Ruffini and Pacinian corpuscles, both endings originating from a single axon. The Ruffini corpuscle, which is morphologically similar to the Golgi tendon organ, is oriented with its long axis in the plane of the skin and forms mechanical linkages with the longitudinally arranged collagen fibers that course through the dermis. The Pacinian corpuscle, which is composed of concentric lamellae around a central core, is situated in deeper layers of the dermis and subcutaneous tissues: the lamellae effectively serve as a high-pass filter, preventing all but the most brisk mechanical events from reaching the generator region of the axon terminal. As discussed below, it is terminal specializations like this that determine how a given sensory axon encodes mechanical stimuli. In addition to these specialized mechanoreceptors, however, free nerve endings – some of which have low thresholds to mechanical stimuli (►tactile C fibers) – are found within the epidermis and dermis. In support of the histological findings, microelectrode recordings from the median and ulnar nerves have also revealed the existence of four classes of low-threshold mechanosensitive afferent in the glabrous skin of the human hand, defined according to their responses to sustained indentation and to the sizes of their receptive fields: two classes of afferent adapt rapidly (►rapidly-adapting afferents type I & II) to a sustained indentation of the skin ("fast-adapting") – types FAI and FAII –and two classes of afferent adapt slowly (►slowly-adapting afferents type I & II) and are referred to as SAI and SAII. Type I afferents possess small, well-defined receptive fields, whereas the receptive fields of the type II afferents are large with poorly defined borders. The most common class encountered in recordings from the median nerve,

which supplies most of the glabrous skin of the hand, is the FAI class, followed by (in descending order) the SAI, SAII and FAII classes [1]. Based on their behavioral similarities with afferents recorded in the cat and monkey it is believed that the FAI afferent – referred to as "RA" (rapidly adapting) in the cat and "QA" (quickly adapting) in the monkey – supplies the Meissner corpuscle, and the SAI afferent the Merkel cell-neurite complex. The receptors belonging to the FAII and SAII afferents are believed to correspond to the Pacinian corpuscle ("PC") and Ruffini ending, respectively.

Non-Glabrous Skin

The hairy skin covers much of the body, and the properties of cutaneous mechanoreceptors supplying this tissue are probably more representative of the "tactile sensory sheet" than those of the glabrous skin – which is rather more specialized. In agreement with the types of receptors found in hairy skin of the cat, five classes of myelinated tactile afferent have been recorded from the lateral antebrachial cutaneous nerve, which supplies the hairy skin of the human forearm: two types of slowly-adapting afferent (SAI & SAII) that can classified in a similar fashion to those in the glabrous skin, and three types of rapidly-adapting afferent – hair units, field units and Pacinian units [2]. Hair units respond specifically to movements of individual hairs and air puffs onto the receptive field, whereas field units respond to actual skin contact; the behavior of the SAI, SAII and FAII units is similar to that observed in glabrous skin, with 80% of the SAII endings presenting a low-level background discharge in the absence of stimulation. The afferent innervation of the skin on the dorsum of the hand, which is supplied by the superficial branch of the radial nerve, is similar to that of the volar surface of the hand: SAI, SAII, FAI and FAII afferents have been identified [3]. However, differences do exist between the two cutaneous regions. Unlike glabrous skin, in which the dominant species of cutaneous afferent is the FAI afferent, two-thirds of the afferents in the hairy skin of the hand are slowly adapting. A further difference lies in the relative proportions of SAI and SAII afferents: in the glabrous skin there are more of the former, whereas there are equivalent numbers in the hairy skin. There are also difficulties in differentiating between SAI and SAII units in the hairy skin, whereas the classifications are quite distinct in glabrous skin. Although few endings associated with hairs have been recorded from the radial nerve this may simply reflect the lower density of hairs on the back of the hand compared with that of the forearm. Nevertheless, a common feature shared by glabrous and non-glabrous skin is the relative paucity of FAII afferents. Microelectrode recordings from the infraorbital nerve have demonstrated that the hairy skin of the human face is innervated by rapidly-adapting and slowly adapting afferents with properties identical to those of the FAI and SAI afferents found in the hand [4]. A distinct population of slowly-adapting afferents that present a very regular discharge characteristic of SAII endings has also been found, although their responsiveness to skin stretch could not be tested. Interestingly, no FAII afferents were encountered; this suggests an absence of Pacinian corpuscles in the human face, and fits with the low sensitivity of the face to high-frequency vibration.

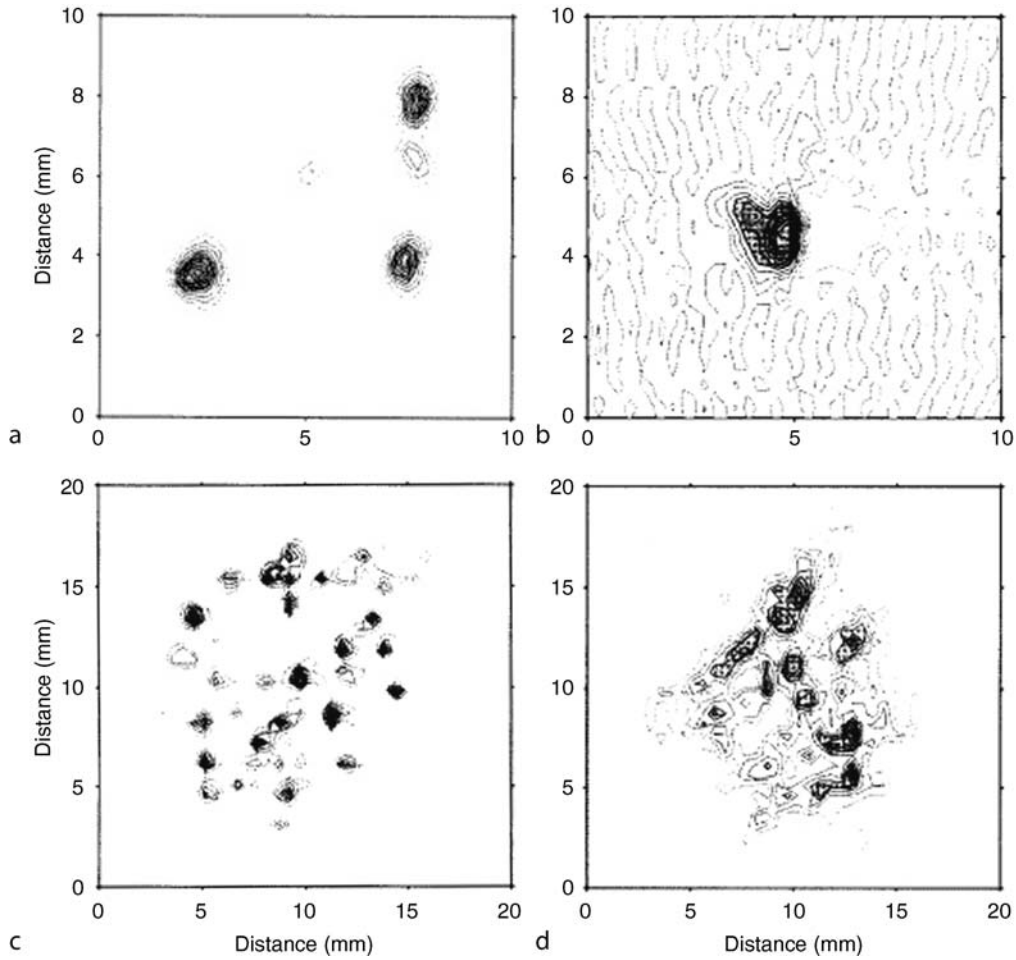
Lower Level Components

Glabrous Skin

Type I tactile afferents have small circular or ovoid receptive fields with distinct borders, and have a higher innervation density in the tips of the digits than more proximally within the hand [1]. In addition, receptive fields are smaller on the distal phalanx of the fingers than on the palm. The receptive field is composed of multiple "hot-spots" in which mechanosensitivity is maximal: FAI afferents contain 12–17 such zones – corresponding to the individual Meissner corpuscles supplied by a single axon – whereas SAI afferents contain only 4–7, corresponding to the individual Merkel cell neurite complexes. Type II afferents have large, poorly-defined receptive fields with obscure borders and, usually, a single zone of maximal sensitivity. In addition, their density is fairly uniform throughout the hand, with the exception of a specific representation of SAII afferents associated with the medial and lateral borders of the nail beds. As noted above, both classes of type II afferent can respond to stimuli applied outside their receptive field: FAII afferents respond to brisk mechanical stimuli and SAII afferents respond to lateral skin stretch; despite their small receptive fields, type I afferents can also respond to stimuli that do not directly engage their receptive field, such as stimuli that compress the finger pad. The mechanical thresholds of each class of afferent, as assessed with calibrated filaments (von Frey hairs), are fairly uniform throughout the glabrous area of the hand, but the rapidly adapting receptors have the lowest thresholds: median thresholds to punctate stimulation are lowest for the FAII (0.54 mN) and FAI (0.58 mN) afferents, and highest for the SAI (1.3 mN) and SAII (7.5 mN) afferents [1].

Non-Glabrous Skin

Receptive field maps of four single cutaneous mechanoreceptors in the hairy skin of the forearm are illustrated in Fig. 1. The fields of the SAI afferents consist of 2–4 distinct islands of high sensitivity separated from each other by 3 mm on average; these spots presumably correspond to the touch domes overlying clusters of Merkel cells (Fig. 1a). On the dorsum of the hand, however, most of the SAI fields (like their



Cutaneous Mechanoreceptors, Functional Behavior. Figure 1 Receptive field maps of single cutaneous mechanoreceptors in the hairy skin of the forearm: (a), SAI afferents with three zones of maximal sensitivity; (b), SAII afferent with single zone of maximal sensitivity; (c), hair unit and, (d), field unit with multiple zones of sensitivity. Note the different scales in C and D. Receptive fields were mapped by scanning the skin with a probe via a computer-controlled X-Y plotter. Reproduced from [2].

rapidly-adapting counterparts) consist of a single spot of maximal sensitivity. Overall, the number of these zones in the hairy skin is lower than in the glabrous skin. Apart from their higher representation in the hairy skin, the SAII afferents are similar to those in the glabrous skin, usually having a single zone of high sensitivity to punctate stimulation (Fig. 1b). Hair units have large ovoid or irregular receptive fields composed of multiple sensitive spots that corresponded to individual hairs (Fig. 1c). On average, each afferent innervates 20 hairs [2]. The field units show a similar arrangement of 10–12 high sensitivity spots encompassed by a similarly large area, although the individual spots are larger and less isolated than those of the hair units. By contrast, on the dorsum of the hand and the hairy skin of the face, the rapidly-adapting afferents have small receptive fields, usually with only a single zone of uniform sensitivity. Mechanoreceptors in the hairy skin of the forearm are exquisitely sensitive, even more so than those in the glabrous skin: after the hair units the afferents with the lowest threshold to von Frey stimulation are the field units, with a median threshold of 0.1 mN; the SAI and SAII afferents have median thresholds of 0.45 and 1.30 mN, respectively [2]. Mechanical thresholds of afferents on the dorsum of the hand and on the face are similar to those in the glabrous skin of the hand [3,4].

Higher Level Processes

Selective stimulation (►microstimulation) of single FAI, FAII and SAI afferents innervating the glabrous skin of the hand evokes elementary sensations of a specific quality [5]. A single pulse delivered to a single FAI afferent can be detected if the subject's attention is directed to it, whereas an SAI afferent requires more

impulses and greater attention. This also fits with the lower mechanical threshold of FAI afferents and confirms an earlier interpretation of psychophysical thresholds that subjects can detect a single impulse generated by a single FAI receptor. Stimulating a single FAI afferent with a low frequency train generates a percept of intermittent tapping that, as the frequency of stimulation increases, becomes one of flutter or vibration; stimulation of a single FAII afferent with a train of pulses always generates a frequency-dependent perception of mechanical vibration. Percepts of sustained pressure can be evoked by selective stimulation of SAI afferents, the magnitude of which increases with increasing stimulation frequency. It would appear that the impulse codes utilized by rapidly and slowly adapting tactile afferents are quite distinct: increasing frequency of stimulation signaling increasing vibration with the former, and increasing pressure with the latter. Stimulation of a single SAII afferent with a train of pulses usually does not elicit a sensation.

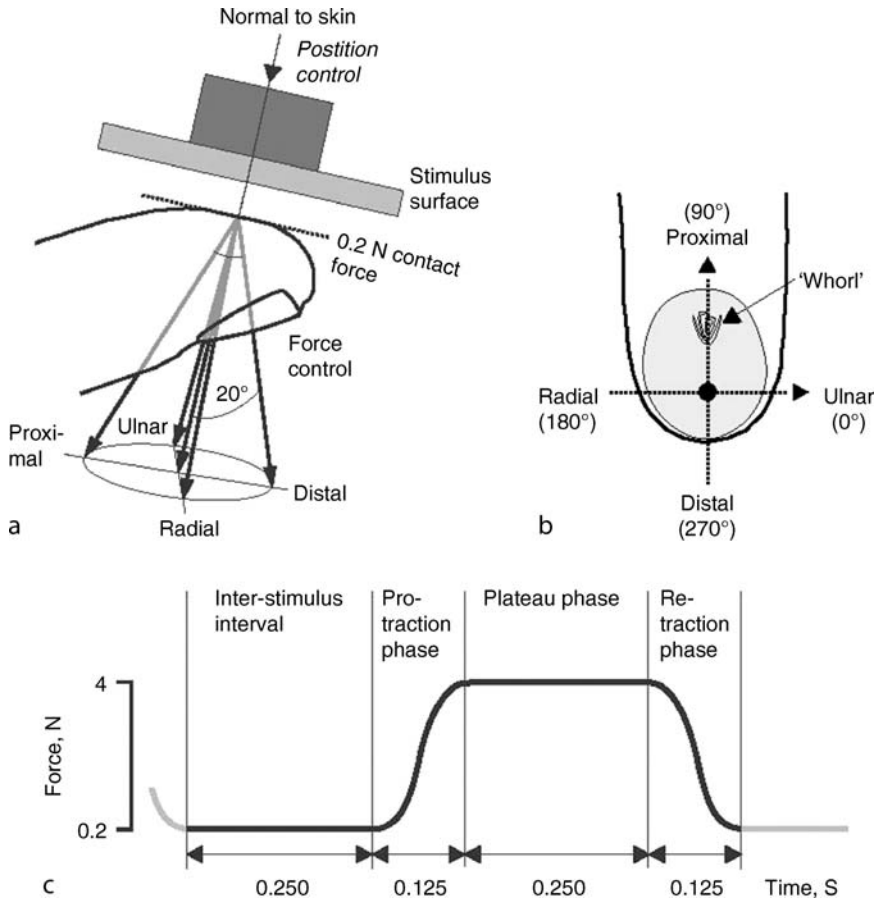
Function

Tactile Sensibility

Because of their low mechanical thresholds, and functional specializations related to anatomic specializations of the receptor endings, tactile afferents contribute importantly to the sensory picture of the body. The afferent innervation of human skin is characterized by regional variations in receptor types and densities that indicate specializations of the "tactile sensory sheet." In the glabrous skin of the hand the tips of the digits contain a high proportion of rapidly-adapting afferents (FAI) with small receptive fields, low mechanical thresholds, and – based on the robust perceptual responses to microstimulation – a secure transmission to the sensory cortex, whereas on the dorsum of the hand these afferents have a much lower representation. FAI afferents can be activated by discrete punctate stimuli in a small, well-defined area of skin; they are particularly sensitive to light stroking across the skin, responding to local shear forces and incipient or overt slips within the receptive field. The rapidly-adapting type II (FAII) afferents, like their PC counterparts in experimental animals, are exquisitely sensitive to brisk mechanical transients: typically, FAII afferents respond to tapping over areas remote from the site of maximal mechanosensitivity, or to blowing over the skin. Instantaneous firing rates are typically higher for the FAII afferents than for the FAI afferents. In all skin areas the numbers of FAII (Pacinian) afferents is low, but given their large field sizes, low thresholds, exquisite sensitivity to mechanical transients and high security transmission to the sensory cortex, their number need not be so high anyway. The slowly-adapting type I afferents (SAI) characteristically have a high dynamic sensitivity to indentation stimuli applied to a discrete area, and often respond with an off-discharge during release. In the glabrous skin of the hand, the SAI endings appear to be of particular importance in encoding shape and – together with the FAI afferents – in fine tactile discrimination. Furthermore, the SAI afferents in the finger pads signal with high fidelity the changes in grip force associated with manipulation of held objects. While the SAII afferents do respond to forces applied normal to the skin, a unique feature of these afferents is their capacity to respond also to lateral skin stretch. Many possess directional sensitivity, the discharge of some afferents increasing with stimuli applied in certain directions, but decreasing in others. And, because SAII afferents possess lower dynamic sensitivity, peak firing rates are typically lower for the SAII afferents than for the SAI afferents. A proportion of SAII afferents are spontaneously active at rest, presenting a characteristically regular discharge. Given their high sensitivity to forces tangential to the skin and poor capacity in spatial discrimination, it is reasonable to conclude that the specific contribution of SAII afferents may lie in signaling changes in conformation of the hand and the load forces (tangential to the skin) encountered during manipulation. The hairy skin of the forearm, which probably typifies the skin of much of the body, has its own specializations: in addition to two classes of very sensitive receptors with large receptive fields (hair units and field units), this region is endowed with non-myelinated mechanosensitive endings of very low threshold (►tactile C fibers).

Although the two classes of rapidly adapting afferent have the lowest thresholds to mechanical stimulation, the slowly adapting type I afferent shares a property with the FAI afferents that effectively increases its mechanosensitivity: FAI and SAI afferents are especially sensitive to edges of a contact surface that crosses the afferent's receptive field. The finger pads have the highest density of FAI and SAI endings; it is this property that endows the finger pads with their exquisite tactile discrimination, and the reason the finger pads are used for tactile exploration and manipulation.

Human subjects have a remarkable capacity to discriminate small differences in forces applied to the finger pad, forces of magnitudes typically associated with manipulation. Recent studies on the responses of tactile afferents in the finger to compression forces applied to the centre of the finger pad (Fig. 2) have emphasized the need to consider receptors in the entire terminal phalanx as providing tactile information on mechanical events in the centre of the pad [6]. Indeed, SAI and SAII endings, as well as FAI receptors, on the end and sides of the terminal phalanx can respond vigorously to stimuli applied at locations remote to their receptive fields, and each of these classes of tactile afferent can contribute to encoding the direction of fingertip forces [6] and the curvature of

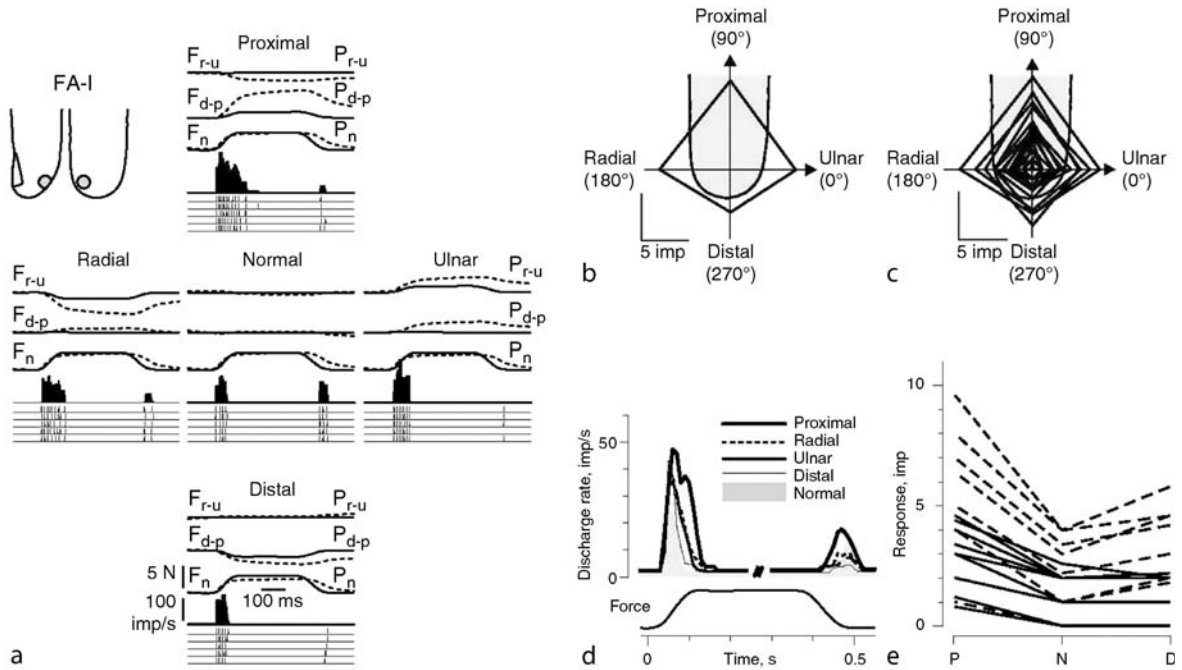


Cutaneous Mechanoreceptors, Functional Behavior. Figure 2 Method of delivering forces to the fingertip in five different directions. (a), The stimulus surface was oriented parallel to the flat portion of skin at the fingertip. Force stimuli were superimposed on a 0.2 N background contact force and delivered in the normal direction and at an angle 20° to the normal with tangential components in the distal, radial, proximal, and ulnar directions as indicated by the *five arrows*; the normal force was always 4 N. (b), Outline of a generic finger showing the stimulation point and the approximate skin area (*shaded*) in contact with the stimulus surface for a 4 N normal force. (c), Temporal profile of the applied forces. Each stimulus consisted of a protraction phase, a plateau phase, and a retraction phase. Reproduced from [6].

objects applied to the finger pad [7]. Directional sensitivity has significant implications for functional specialization and, surprisingly, is present for each class of tactile afferent. Figure 3 show the directional sensitivity of FAI afferents in the distal phalanx of the finger to forces applied to the centre of the finger pad according to Fig. 2.

Sensorimotor Control of the Hand

Cutaneous mechanoreceptors in the fingers are critical for fine sensorimotor control of the hand. People with impaired tactile sensibility of the fingers (including that associated with aging) show clumsiness during object manipulation tasks: objects are frequently dropped, fragile objects may be crushed, and they have severe problems in stereognostic discrimination of objects. Most previous studies of afferents from the glabrous skin of the human hand have addressed issues related to use of the hand in exploratory tasks, with comparatively little research devoted to the tactile encoding of the various mechanical fingertip events critical for the control of dextrous manipulation. The responses of human tactile afferents in relation to discrete motor control events were demonstrated for the first time during object lifting [8] and restraint tasks [9]. The neural programs involved in the sensorimotor control of manipulation are tuned parametrically to the physical properties of the object, whether this be surface friction and object mass, mass distribution or the shape of grasped surfaces. Through *Anticipatory Parameter Control* people use implicit memories from previous manipulatory experiences to retrieve internal models pertaining to the relevant properties of the target objects. Importantly, tactile signals from the

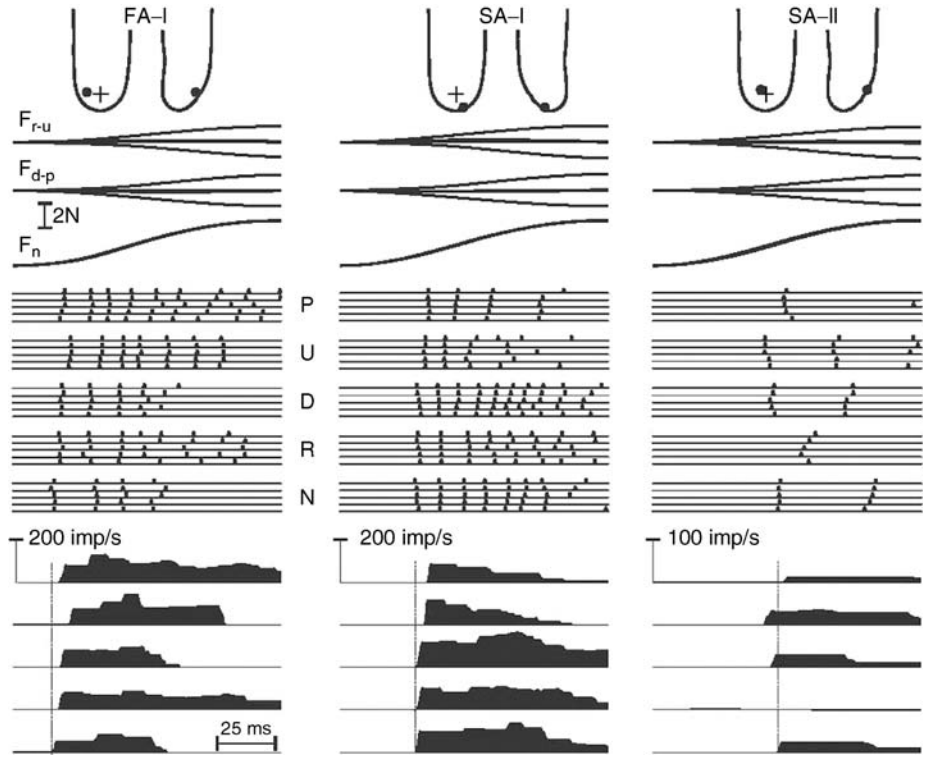


Cutaneous Mechanoreceptors, Functional Behavior. Figure 3 Responses of FAI afferents to servo-controlled forces applied in five directions. (a), Responses of a single FAI afferent which responded preferentially to forces delivered in the proximal direction (b), The generic finger outline shows a polar plot for the afferent illustrated in A. (c–e), Data from 21 afferents for which response was greatest when the tangential component of force was in the proximal direction. (c), Overlaid polar plots, superimposed on the generic finger, for the 21 afferents for which responses were greatest when the tangential component of force was in the proximal direction. (d), Instantaneous firing rates, averaged over the five trials, for the same 21 afferents as in C, shown for forces with tangential components in the four directions and for normal force stimulation. (e), For each of the 21 afferents in C, lines join three data points representing the response, averaged over the five trials, to forces in the proximal (P), normal (N), and distal (D) directions. Reproduced from [6].

fingertips play a key role for the forming and updating those models. Through *Discrete Event, Sensory-driven Control* the time-varying tactile inflow is compared with an internal signal representing the predicted sensory outcomes (also generated by the active sensorimotor program). Disturbances in task execution due to erroneous parameter specification are reflected in a mismatch between predicted and actual sensory input; discrete tactile events may not occur when expected, or alternatively, they may occur unexpectedly. When such a mismatch is detected, pre-programmed patterns of corrective responses are triggered, along with an update of the parameter specification of the relevant internal model. For friction and aspects of object shape this updating primarily occurs during the initial contact with the object; tactile afferents in the finger pads provide this information.

An astonishing feature of sensorimotor control of hand is the speed with which motor commands are parametrically updated in response to discrete mechanical events during object manipulation. It appears that tactile information from the fingertips is already available when most afferents would have had time to fire only one nerve impulse. Thus, besides traditional coding mechanisms based on rate codes requiring several or at least two impulses per afferent, a new much faster coding mechanism based on first spike latencies has been proposed [10]. This study demonstrated that the sequence in which different afferents initially discharge may provide information about the force directions and shape of grasped surfaces faster than any rate code and matches the speed with which this information is utilized by the sensorimotor control loops. Signals provided by FAI afferents are most efficient in this capacity, followed by the SAI afferents (Fig. 4).

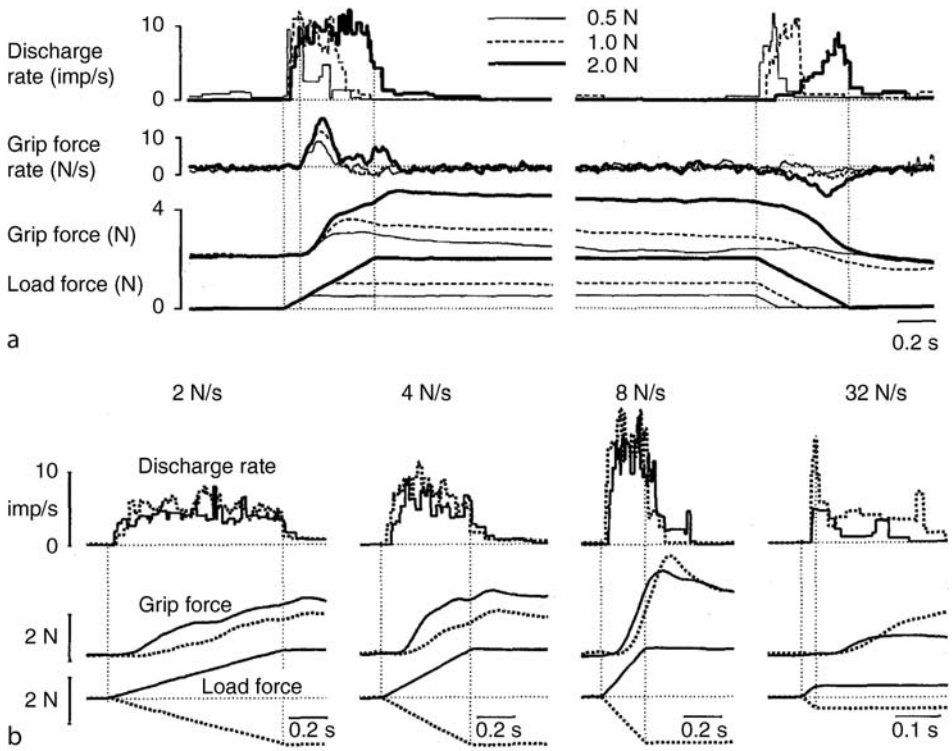
When holding an object between the fingers and thumb there are two primary forces that act at the skin: a compressive component normal to the skin and a shear component tangential to the skin. The first is brought about by the grip forces exerted by the muscles acting on the digits, the second by the effect of gravity on the held object or any other net force imposed by the object or hand on the object. Johansson and colleagues



Cutaneous Mechanoreceptors, Functional Behavior. Figure 4 Modulation of first spike latencies by direction of fingertip force. Responses of single afferents of each type to the proximal ("P"), ulnar ("U"), distal ("D"), radial ("R") direction and with normal force ("N") only (see stimuli in Fig. 2). Impulse ensembles show responses to the repeated stimuli (n = 5). Traces above show the normal force (F_n) and tangential forces in the radial-ulnar (F_{r-ul}) and distal-proximal (F_{d-p}) directions, superimposed for all trials; traces below show the instantaneous discharge frequency averaged over the five trials. Vertical lines indicate the response onset latency for stimulation with normal force, i.e., the condition labeled "N." Symbols on the finger outlines indicate the centers of the afferents' receptive fields. Reproduced from [10].

have shown that cutaneous afferents in the glabrous skin of the digits are capable of encoding the grip and load forces associated with grasping and lifting an object, and that the information provided by tactile afferents to the central nervous system is of paramount importance in the fine coordination of load and grip forces [8]. When grasping and lifting a passive object between finger and thumb the type I afferents (FAI and SAI) in the tips of the digits respond with high firing rates at the moment of contact and in the early part of the loading phase, during which the grip force increases in parallel with the load force at a rate sufficient to prevent slipping of the object. The FAI and SAI afferents also respond to local mechanical disturbances during the lifting and hold phases, such as incipient or overt slips. FAII afferents respond to the mechanical transients associated with initial contact and release of the object, and they are especially sensitive to the acceleration (and deceleration) signals related to the start and end of a grip and lift (or replace) movement sequence. The SAII afferents generally respond to the grip force during the loading and hold phases of the lift, and also to the tangential loads generated at the skin during the hold phase.

Similar behavior is observed when subjects attempt to prevent escape of a manipulandum from the grasp during unexpected increases or decreases in tangential force: the FAI, SAI and SAII afferents in the finger pads respond to the shear forces generated between the skin and the manipulandum, but the FAII afferents do not respond to these slow events. While the slowly-adapting afferents also respond during the subsequent increases in grip force that serve to restrain the manipulandum, as shown in Fig. 5, FAI afferents respond only during the dynamic phases of the stimulus, i.e., during the loading and unloading ramps, and less to the normal forces associated with the increase in grip force [9]. Tactile afferents also provide information on the rotational forces associated with manipulation of held objects. Indeed, torque loads tangential to the fingertips are common in the majority of natural manipulatory tasks. Everyday tasks, such as lifting a book from the shelf by its spine, would not be possible if the motor control system did not automatically coordinate grip forces with torsional



Cutaneous Mechanoreceptors, Functional Behavior. Figure 5 Mean responses of 8 FAI afferents in the finger pads to tangential loads applied to the receptor-bearing digit at, (a), a constant ramp rate delivered at three different amplitudes (0.5–2.0 N) and, (b), at four ramp rates (2–32 N/s) delivered at a constant amplitude (2 N). Subjects gripped an instrumented manipulandum which delivered, at unexpected times, tangential loads in the distal (upward = pulling) or proximal (downward = pushing) direction. Reproduced from [9].

loads. Torque loads depend on rotational (torsional) friction between the fingertips and the object, which arises because the normal force is distributed across the skin-object contact area, rather than focused at a point. Thus, to prevent an object from slipping under combined linear force and torque loads, we need to apply a grip force that is higher than that required to prevent slips due to the linear load force only. Surface curvature parametrically scales the relationship between the grip force and tangential torque: the grip force at any given tangential torque increases with increasing surface convexity and thereby prevents rotational slips. Again, tactile afferents in the finger pads provide this information.

Pathology

Loss of cutaneous (and proprioceptive) sensibility can occur in rare large-fiber sensory neuropathies. Patients loose all discriminative touch and their capacity for fine motor control, relying on vision as the only source of feedback. Nevertheless, in the hairy skin they do have preserved C-fiber function and, because of the low-threshold C-fibers (▶tactile C fibers), can sense light stroking on the skin.

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Cutaneous Reflexes

Definition

An automatic and stereotypical response to cutaneous stimulation that is mediated through a polysynaptic set of interneurones in the spinal cord. A cutaneous reflex may be elicited by stimulation of any cutaneous sensory organs, broadly classified as innocuous mechanoreceptors, innocuous thermoreceptors, and nociceptors.

►Integration of Spinal Reflexes

CVA Brain Attack

►Stroke

Cyborg

Definition

Contraction of Cybernetic Organism. Organism composed of a living and an artificial portion, in close bidirectional interaction. The term was first introduced in 1960 by Clynes and Kline in the context of the debate on humans colonizing space. If man in space, in addition to flying his vehicle, must continuously be checking on things and making adjustments merely in order to keep himself alive, he becomes a slave to the machine. The purpose of the Cyborg, as well as his own homeostatic systems, is to provide an organizational system in which such robot-like problems are taken care of automatically and unconsciously, leaving man free to explore, to create, to think, and to feel (Clynes & Kline 1960).

►Computer-Neural Hybrids

Cycle

Definition

The complete sequence of values of a periodic quantity that occur during a period.

Cyclic AMP

Definition

3-5-cyclic adenosine monophosphate (cAMP, formed from adenosine triphosphate, ATP, by the action of the enzyme adenylyl cyclase) is a second messenger, used for intra-cellular signal transduction of some inter-cellular messages (some hormones and neurotransmitters) or sensory messages such as odorants which cannot get through the cell membrane. These messages are also called “first messengers”.

Cyclic AMP- and cGMP-dependent Protein Kinases (cAKs, cGKs)

Definition

These enzymes are activated by the binding of cAMP or cGMP. When activated cAKs and cGKs phosphorylate specific serine or threonine residues in target proteins and thereby control the activity of these proteins.

►Cyclic Nucleotide-regulated Cation Channels

Cyclic AMP-binding Guanine Nucleotide Exchange Factors (cAMP-GEFs)

Definition

In the cAMP-bound conformation cAMP-GEFs specifically bind to Ras-like small G proteins and activate these proteins by profoundly accelerating the exchange of GDP for GTP.

►Cyclic Nucleotide-regulated Cation Channels

Cyclic GMP

Definition

Cyclic guanosine monophosphate (cGMP) is an intracellular second messenger generated by guanylyl cyclase from guanosine triphosphate (GTP).

Cyclic GMP-regulated Phosphodiesterases

Definition

Phosphodiesterases represent a multi-gene family of enzymes that hydrolyze the second messengers cGMP and cAMP. The hydrolytic activity of several sub-families of these enzymes is regulated in an allosteric manner by the binding of cGMP. Notably, the cyclic nucleotide binding site present in cGMP-regulated phosphodiesterases is not homologous to that found in most other cyclic nucleotide-binding proteins.

►Cyclic Nucleotide-regulated Cation Channels

Cyclic Nucleotide-binding Domain (CNBD)

Definition

In cyclic nucleotide-regulated channels this domain serves as a high-affinity binding site for 3–5 cyclic monophosphates. The CNBD of channels has significant sequence similarity to the CNBDs of most other classes of eukaryotic cyclic nucleotide receptors and to the CNBD of the prokaryotic catabolite activator protein (CAP). The primary sequence of CNBDs consists of approximately 120 amino acid residues forming three α-helices (αA–αC) and eight β-strands (β1–β8).

►Cyclic Nucleotide-Regulated Cation Channels

Cyclic Nucleotide-gated Cation Channel

Definition

►Cyclic Nucleotide-regulated Cation Channels

Cyclic Nucleotide-regulated Cation Channels

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Synonyms

CNG channels; HCN channels

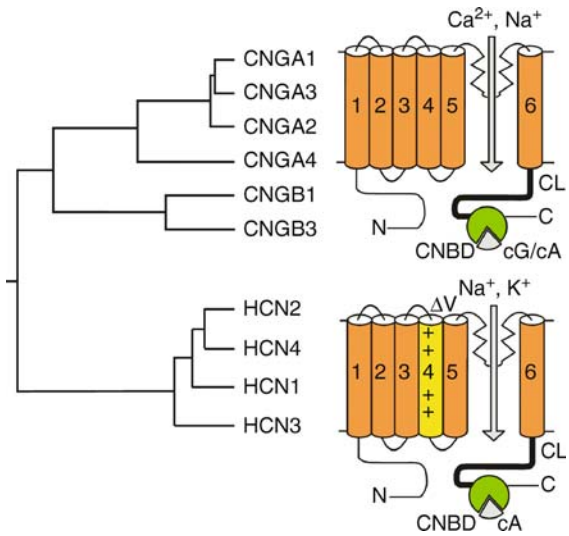
Definition

Cyclic nucleotide-regulated cation channels are ion channels whose activation is regulated by the direct binding of cyclic AMP or cyclic GMP to the channel protein. Two families of channels regulated by cyclic nucleotides have been identified, the cyclic nucleotide-gated (CNG) channels [1,2] and the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels [3–5]. CNG channels require the obligatory binding of a cyclic nucleotide in order to be activated. In contrast, HCN channels are activated by membrane hyperpolarization. Cyclic nucleotides enhance HCN channel activity by affecting the voltage-dependence of channel activation.

Characteristics

Cyclic nucleotides exert their cellular effects by binding to four major classes of cellular receptors: ►Cyclic AMP- and cGMP-dependent protein kinases (cAKs, cGKs), ►Cyclic GMP-regulated phosphodiesterases, ►Cyclic AMP-binding guanine nucleotide exchange factors (cAMP-GEFs) and cyclic nucleotide-regulated cation (CNG and HCN) channels. Cyclic nucleotide-regulated cation channels are unique among these receptors because their activation is coupled to the influx of extracellular cations into the cytoplasm and to the depolarization of the plasma membrane. CNG channels pass monovalent cations, such as Na^+ and K^+, but do not discriminate between them. Calcium is also permeable but at the same time acts as a voltage-dependent blocker of monovalent cation permeability. By providing an entry pathway for Ca^{2+}, CNG channels control a variety of cellular processes that are triggered by this cation. HCN channels conduct Na^+ and K^+ with permeability ratios of about 1:4 and are blocked by millimolar concentrations of Cs^+. Despite this preference for K^+ conductance, HCN channels carry an inward Na^+ current under physiological conditions. HCN channels can also conduct Ca^{2+}, but not as well as CNG channels. At 2.5 mM external Ca^{2+}, the fractional Ca^{2+} current of HCN2 and HCN4 is about 0.5%, whereas for native CNG channels it is in range between 10 and 80%.

CNG and HCN channels belong to the superfamily of ►voltage-gated cation channels. The proposed structure of the channels is shown in Fig. 1. The transmembrane channel core consists of six α-helical segments (S1 –S6) and an ion-conducting ►pore loop between the S5 and S6. The amino- and carboxy-termini are localized in the cytosol. CNG and HCN channels contain a positively charged S4 helix carrying three to nine regularly spaced arginine or lysine residues at every third position. In HCN channels, as in most other members of the channel superfamily, the S4 helix functions as "voltage-sensor" conferring voltage-dependent ►gating. In CNG channels, which are only slightly voltage-dependent, the specific role of S4 is not known. In the carboxy-terminus, CNG and HCN channels contain a ►cyclic nucleotide-binding domain (CNBD) that is homologous to CNBDs of cAKs, cGKs and cAMP-GEFs. In CNG channels, the binding of cGMP or cAMP to the CNBD initiates a sequence of allosteric transitions that lead to the opening of the ion-conducting pore. In HCN channels, the binding of cyclic nucleotides is not required for activation. However, cyclic nucleotides shift the voltage-dependence of channel activation to a more positive membrane potential and thereby facilitate voltage-dependent channel activation. CNG and HCN channels are tetramers. In native tissue, HCN channel subunits can assemble to form either homo- or heteromeric complexes. By contrast, all known native CNG channels are heterotetramers.



Cyclic Nucleotide-regulated Cation Channels.
Figure 1 Phylogenetic tree and structural model of cyclic nucleotide-regulated cation channels. The CNG channel family comprises six members, which are classified into A subunits (CNGA1 –4) and B subunits (CNGB1 and CNGB3). A "CNGB2" subunit does not exist. The HCN channel family comprises four members (HCN1 –4). CNG and HCN channels share the same transmembrane topology, consisting of six transmembrane segments (1 –6), a pore loop and a cyclic nucleotide-binding domain (CNBD). CNG channels conduct Ca^{2+} and Na^{+} whereas HCN channel mainly conduct Na^{+} and K^{+}. CNG channel are activated *in vivo* by binding of either cAMP (cA) or cGMP (cG), depending on the channel type. HCN channels activate on membrane hyperpolarization (ΔV), and are enhanced by binding of cAMP. The positively charged amino acid residues in the S4 segment of HCN channels are indicated by + symbols. CL, C-linker involved in activation gating of CNG and HCN channels.

CNG Channels

CNG channels are expressed in retinal photoreceptors and olfactory neurons and play a key role in visual and olfactory signal transduction. In addition, CNG channels are found at low density in some other cell types and tissues such as brain, testis and kidney. While the function of CNG channels in sensory neurons has been unequivocally demonstrated, the role of these channels in other cell types where expression has been observed remains to be established. Based on their phylogenetic relationship, the six CNG channels identified in mammals are divided in two subfamilies, the A-subunits (CNGA1 –4) and the B-subunits (CNGB1 and CNGB3). When expressed in ►heterologous expression systems, A-subunits, with the exception of CNGA4, form functional homomeric channels. In contrast, B-subunits do not give rise to functional channels when expressed alone. However, together with CNGA1 –3 they confer novel properties (e.g. single channel flickering, increased cAMP sensitivity) that are characteristic of native CNG channels. In native tissues, CNG channels are heterotetramers with different heteromers displaying distinct nucleotide sensitivity, ion selectivity and modulation by Ca^{2+}. Recent genetic studies in mice indicate that B-subunits play a key role in principal channel formation and channel targeting in native sensory neurons. For example, mice lacking the CNGB1 subunit fail to express substantial amounts of CNG channels in rod outer segments and olfactory cilia, respectively. The physiological role and subunit composition is known for three native channels: the rod and cone photoreceptor channels and the olfactory channel. The CNG channel of rod outer segment consists of the CNGA1 subunit and the CNGB1a subunit (3:1 stoichiometry). The cone photoreceptor channel consists of the CNGA3 and the CNGB3 subunit (2:2 stoichiometry). CNG channels control the membrane potential and the calcium concentration of

photoreceptors. In the dark, the channels are maintained in the open state by a high concentration of cGMP. The resulting influx of Na^+ and Ca^{2+} (dark current) depolarizes the photoreceptor and promotes synaptic transmission. Light-induced hydrolysis of cGMP leads to the closure of CNG channels. As a result the photoreceptor hyperpolarizes and shuts off synaptic glutamate release. Mutations in human CNG channel genes have been linked to retinal diseases. Mutations in the CNGA1 and CNGB1 subunits have been identified in the genome of patients suffering from ►retinitis pigmentosa. The functional loss of either the CNGA3 or the CNGB3 subunit causes total color blindness (achromatopsia) and degeneration of cone photoreceptors.

The olfactory CNG channel consists of three different subunits: CNGA2, CNGA4 and the CNGB1b subunit (2:1:1 stoichiometry). The channel is activated *in vivo* by cAMP which is synthesized in response to the binding of odorants to their cognate receptors. The olfactory CNG channel mainly conducts Ca^{2+} under physiological ionic conditions. The increase in cellular Ca^{2+} activates a Ca^{2+}-activated Cl^-channel which further depolarizes the cell membrane. Ca^{2+} is not only a permeating ion of the olfactory CNG channel, it also represents an important modulator of this channel. By forming a complex with calmodulin, which binds to the CNGB1b and CNGA4 subunit, Ca^{2+} decreases sensitivity of the CNG channel to cAMP. The resulting inhibition of channel activity is the principal mechanism underlying fast odorant adaptation.

HCN Channels

A cation current that is slowly activated by membrane hyperpolarization (termed I_h, I_f or I_q) is found in a variety of excitable cells including neurons, cardiac pacemaker cells and photoreceptors. The best understood function of I_h is to control heart rate and rhythm by acting as "pacemaker current" in the sinoatrial (SA) node. I_h is activated during membrane hyperpolarization following the termination of an action potential and provides an inward Na^+ current that slowly depolarizes the plasma membrane. Sympathetic stimulation of SA node cells raises cAMP levels and increases I_h by a positive shift of the current activation curve, thus accelerating diastolic depolarization and heart rate. Stimulation of muscarinic receptors slows down heart rate by the opposite action. In neurons, I_h fulfills diverse functions, including generation of pacemaker potentials (neuronal pacemaking), control of membrane potential, generation of rebound depolarizations during light-induced hyperpolarizations of photoreceptors, dendritic integration, and synaptic transmission.

HCN channels represent the molecular correlate of the I_h current. In mammals, the HCN channel family comprises four members (HCN1 –4) that share about 60% sequence identity to each other and about 25% sequence identity to CNG channels. The highest degree of sequence homology between HCN and CNG channels is found in the CNBD. The crystal structure of this domain has been determined for HCN2 and a bacterial CNG channel. When expressed in heterologous systems all four HCN channels generate currents displaying the typical features of native I_h: (i) activation by membrane hyperpolarization, (ii) permeation of Na^+ and K^+ with a permeability ratio P_{Na}/P_K of about 0.2, (iii) modulation of voltage-dependence of channel activation by direct binding of cAMP, (iv) channel blockade by extracellular Cs^+.

HCN1 –4 mainly differ from each other with regard to their speed of activation and the extent by which they are modulated by cAMP. HCN1 is the fastest channel, followed by HCN2, HCN3 and HCN4. Unlike HCN2 and HCN4, whose activation curves are shifted by about +15 mV by cAMP, HCN1 and HCN3 are only weakly, if at all, affected by cAMP.

Site-directed mutagenesis experiments have provided insight into the complex mechanism underlying dual HCN channel activation by voltage and cAMP. Like in other voltage-gated cation channels, activation of HCN channels is initiated by the movement of the positively charged S4 helix in the electric field. The resulting conformational change in the channel protein is allosterically coupled by other channel domains to the opening of the ion-conducting pore. Major determinants affecting channel activation are the intracellular S4 –S5 loop, the S1 segment and the extracellular S1 –S2 loop. The CNBD fulfils the role of an autoinhibitory channel domain. In the absence of cAMP the cytoplasmic carboxy-terminus inhibits HCN channel gating by interacting with the channel core and, thereby, shifting the activation curve to more hyperpolarizing voltages. Binding of cAMP to the CNBD relieves this inhibition. Differences in the magnitude of the response to cAMP among the four HCN channel isoforms are largely due to differences in the extent to which the CNBD inhibits basal gating. It remains to be determined if the inhibitory effect of the CNBD is conferred by a direct physical interaction with the channel core domain or by some indirect pathway. There is evidence that the so-called C-linker, a peptide of about 80 amino acids that connects the last transmembrane helix (S6) to the CNBD plays an important role in this process. The C-linker was also shown to play a key role in the gating of CNG channels, suggesting that the functional role of this domain has been conserved during channel evolution.

HCN channels are found in neurons and heart cells. In mouse and rat brain all four HCN isoforms have been detected. The expression levels and the

regional distribution of the HCN channel mRNAs vary profoundly between the respective channel types. HCN2 is the most abundant neuronal channel and is found almost ubiquitously in the brain. In contrast, HCN1, HCN3 and HCN4 are enriched in specific regions of the brain such as thalamus (HCN4) hippocampus (HCN1) or olfactory bulb and hypothalamus (HCN3). HCN channels have also been detected in the retina and some peripheral neurons such as dorsal root ganglion neurons. In SA node cells, HCN4 represents the predominantly expressed HCN channel isoform. In addition, minor amounts of HCN2 and HCN1 are also present in these cells. Insights into the (patho) physiological relevance of HCN channels have been gained from the analysis of mouse lines lacking individual HCN channel isoforms. Disruption of HCN1 impairs motor learning but enhances spatial learning and memory. Deletion of HCN2 results in absence epilepsy, ataxia and sinus node dysfunction. Mice lacking HCN4 die *in utero* due to the failure to generate mature sinoatrial pacemaker cells. The key role of HCN4 in controlling heart rhythmicity is corroborated by genetic data from human patients. Mutations in the human HCN4 gene leading to mutated or truncated channel proteins have been found to be associated with sinus bradycardia (S672R, 573X) and complex cardiac arrhythmia (D552N).

Drugs Acting on CNG Channels

Several drugs have been reported to block CNG channels. The most widely used among these drugs is L-*cis* diltiazem which blocks CNG channels in a voltage-dependent manner at micromolar concentrations. The D-*cis* enantiomer of diltiazem, which is an important therapeutic blocker of the L-type calcium channel, is much less effective than the L-*cis* enantiomer in blocking CNG channels. High affinity binding of L-*cis* diltiazem is only seen in heteromeric CNG channels containing the CNGB1 subunit. CNG channels are also moderately sensitive to blockage by some other inhibitors of the L-type calcium channel (e.g. nifedipine), the local anesthetic tetracaine and calmodulin antagonists. Interestingly, LY83583 [6-(phenylamino)-5,8-quinolinedione] blocks both the soluble guanylyl cyclase and some CNG channels at similar concentrations. H-8 [N-2-(methylamino)ethyl-5-isoquinolinesulfonamide], which has been widely used as a non-specific cyclic nucleotide-dependent protein kinase inhibitor, blocks CNG channels, though at significantly higher concentrations than needed to inhibit protein kinases. The most potent blocking agent for CNG channels is pseudechetoxin. This toxin inhibits homomeric CNGA2 channels with a K_i of 5 nM and the homomeric CNGA1 channel with a K_i of 100 nM. The peptide is several orders of magnitude less effective in blocking the heteromeric channels.

Drugs Acting on HCN Channels

Given the key role of HCN channels in cardiac pacemaking, these channels are promising pharmacological targets for the development of drugs used in the treatment of cardiac arrhythmias and ischemic heart disease. HCN channels are not expressed in vascular and airway smooth muscle. As a consequence, specific HCN channel blockers are expected to have no side effect on the peripheral resistance. Importantly, unlike the well-established β-adrenoceptor blockers, HCN channel blockers would not impair pulmonary function in patients with asthma or obstructive pulmonary disease. Recently, ivabradine (S16257, Procoralan) was approved as the first therapeutic I_h blocker. Ivabradine blocks cardiac I_h at low micromolar concentrations and is used in the treatment of stable angina pectoris. Other known I_h blockers with blocking mechanisms related to that of ivabradine are ZD7288 [4-(N-ethyl-N-phenylamino)-1,2-dimethyl-6-(methylamino)pyrimidinium chloride], zatebradine and cilobradine. These blocker were not introduced into therapy because they either lacked specificity or exerted unacceptable side effects, in particular visual disturbances due to the inhibition of retinal I_h. Interestingly, the well-known α_2 adrenoceptor agonist clonidine also effectively blocks HCN channels. The block of cardiac I_h (mainly conferred by HCN4) contributes significantly to the bradycardic effect of clonidine. Modulation of I_h may also be a promising approach for treatment of disease processes in central and peripheral nervous system. For example, I_h is upregulated in dorsal root ganglion neurons in response to nerve injury making HCN channels interesting candidates for therapeutic modulation of inflammation and neuropathic pain. Moreover, agents acting on HCN channels may be utilized in the treatment of epilepsies. Finally, HCN1 and HCN2 channels are inhibited by clinically relevant concentrations (≤0.5 mM) of the inhalational anesthetics halothane and isoflurane. Similarly, the intravenous anesthetic propofol inhibits and slows the activation of native and expressed HCN channels. Thus, modulation of I_h may contribute to clinical actions of anesthetic agents.

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Cyclins

Definition

Family of proteins that regulate the progress of cells through the cell cycle.

Cyclooxygenase-2

Definition

The cyclooxygenase (COX)-2 enzyme catalyzes the conversion of arachidonic acid into prostaglandins. The type-2 isoform of COX is induced during injury and infection. COX-2 generated prostaglandins induce inflammatory pathways, pain and fever.

►Central Nervous System Inflammation: Astroglia and Ethanol

Cys-Loop Receptors

Definition

Members of the Cys-loop receptor class are ligand-gated ion channels that open in response to binding of ACh, 5-HT (serotonin), Glycine, GABA. Cys loop receptor channels form from homo- or hetero-tetrameric arrangement of subunits surrounding an aqueous pore. Each subunit consists of an extracellular aminoterminal domain, followed by four transmembrane segments. They harbor a signature sequence of 13 residues flanked by cysteins which form a closed loop linking the extracellular ligand binding and channel domains.

►Acetylcholine
►GABA
►Glycine
►Ion Channels from Development to Disease
►Serotonin

Cystometry

Definition

Cystometry is the study of urinary bladder activity by recording the intravesical pressures exerted at varying degrees of bladder filling with water or gas.

►Micturition, Neurogenic Control

Cytoarchitecture

Definition

Refers to the morphological characteristics of cells.

►Evolution of the Brain: in Birds

Cytokines

Definition

The loose definition of cytokines is that they are proteins made by cells that affect the behavior of other cells through actions on specific cytokine receptors. The term is often used in a narrower sense as messages produced by white blood cells that affect the behavior of other blood cells and other non-blood cells. The term can therefore encompass neurotrophic factors, or may be used to refer only to cells released by lymphocytes, macrophages/microglia and polymorphs. In neurobiology the term is increasingly being used to refer to all small, low-molecular-weight (usually less then 30 kDa in size) protein messengers for inter-cell communication. Cytokines are also involved with inflammatory and hypersensitive reactions. They are critical to the functioning of both the innate and adaptive immune responses to injury in

many cell and tissue types. Usually cytokines are not produced at high levels in normal resting conditions but are rapidly and transiently up-regulated following appropriate stimuli. Cytokines exert their biological effect by interacting with high-affinity cell surface metabotropic receptors, leading to an intracellular cascade of signalling events and activation of transcription factors.

►Neurotrophic Factors

Cytoplasmic mRNA Localization

►mRNA Targeting: Growth Cone Guidance

Cytoskeleton

Definition

The cytoskeleton of a cell is the framework that gives the cell its shape and integrity. It is also involved in the movement of organelles, and it plays an important role in cell division. Important cytoskeletal proteins are the microfilament actin, the intermediate sized neurofilament and the microtubules.

►Actin
►Microtubule
►Neurofilament