Central control of autonomic function

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Abstract

In this review, current understanding of the control of autonomic function is outlined and its development over the last 50 years highlighted. Using the control of the cardiovascular system as the primary tool, the importance of the patterning of autonomic outflows is shown to be crucial in both homeostasis and behaviour. Technical advances have made it possible to obtain a clearer idea of how the central nervous system evolves patterns of autonomic discharge that optimise autonomic changes to support motor and behavioural responses. The specific roles of sympathetic and parasympathetic preganglionic neurones and premotor neurones are surveyed and the importance of their roles in integrating afferent inputs that result from peripheral sensory inputs and drive from multiple levels of the neuraxis is outlined. The autonomic control of the viscera, including the urinogenital organs and other organs is discussed briefly. The current ability to use animal models to monitor and modulate autonomic neural discharge and simultaneously co-relate this with end-organ activity is shown to have translational potential. There is every prospect that these studies will lead to the identification of new therapies for pathophysiological conditions.

Introduction

In the 50 years since the founding of *Brain and Neuroscience Advances* (BNA), autonomic neuroscience has advanced in parallel with growth of the whole field of neuroscience. This has been not only through the application of ever more sophisticated techniques but also through the development of new ideas. We now recognise the system is not simply concerned with homeostasis. It is a system that is regulated both through modality-specific afferents and their reflex circuits and by functionally selective groups of neurones with increasing degrees of complexity at all levels of the central nervous system (CNS).

At the time of the foundation of the BNA, there was a reappraisal of the nature of central autonomic control. A particular inspiration for this critical change came from the work of the Hilton laboratory in the 1960s. Hilton and colleagues demonstrated that the cardiovascular changes elicited by stimulation at specific sites in the brain could elicit cardiovascular changes that were identical to those seen in defensive behaviour (Abrahams et al., 1960; Hilton, 1982). Furthermore, stimulation of these same sites in the freely moving animal elicited the same cardiovascular responses but also evoked defensive behaviour. These observations challenged the dogma that cardiovascular control and particularly that of blood pressure was regulated through centres in the lower brainstem that were specific to cardiovascular control.

As scientists who were part of the Hilton laboratory, we will in this review mainly use the autonomic control of the cardiovascular system as a model to demonstrate the new concepts that

have developed. We will also briefly refer to other autonomic functions and will hope to provide an indication of how the technical advances available to neuroscientists have given us the tools to develop a contemporary knowledge that is leading to translational studies with the potential to address clinical problems.

Autonomic patterns

It became clear that all behavioural functions like feeding, drinking, exercise, sex, body temperature, micturition, defaecation and even major sensory functions require quite precise, selective and differential patterns of autonomic nerve activity (Janig, 2006). Such autonomic actions are mediated by intrinsic plexuses of neurones and postganglionic nerves supplying the smooth muscle of the eye, blood vessels, the airways, urinary system, gut, sex

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organs, the heart, secretory glands, sweat glands and hairs of the skin, endocrine tissue, immune system and the catecholamine releasing cells of the adrenal medulla. This implies that a pattern of response to a particular sensory challenge requires specific functional and anatomical connections from modality-specific sources. Evidence shows that interaction of peripheral and central afferents provide convergent inputs on organ-specific neurones at various levels of the CNS and therefore represent an organisational structural principle of the autonomic nervous system (ANS).

Preganglionic organisation

In accordance, at a spinal level, functionally distinct groups of autonomic preganglionic neurones are identified in columns at precise locations in the grey matter of thoracic, lumbar and sacral regions (Janig, 2006). It became clear that these *preganglionic* neurones not only form the final projection from the CNS to the postganglionic neurones in peripheral ganglia which projects to the target sites but also have a major role in integrating synaptic input from supraspinal regions. A particularly important discovery was that spinal afferent fibres do not make direct monosynaptic connections with these preganglionic neurones but mainly connect via long pathways to and from the brainstem and suprabulbar regions (Coote, 1988). It was shown that elicitation of functional patterns coupled to both motor and emotional responses involving several target organs including cardiovascular ones depended on signals in modality-specific sensory pathways that effect the excitability of different groups of brain neurones such as those involved in exercise (Coote, 1995) feeding (Janig, 2006), urinary bladder continence (De Groat, 2011) and sex (Marson, 2011), among others.

Therefore, inhibitory and excitatory effects are processed by preganglionic neurones in the brainstem for cranial parasympathetic, in spinal thoracolumbar region for sympathetic and in sacral region for spinal parasympathetic outflow.

Attention became focussed on electrophysiologically identifying autonomic preganglionic neurones and studying their synaptic inputs (Coote, 1988; Janig, 2006). Autonomic neurones can be distinguished from other motoneurones by the distinctive range of cation ion channels that they express.

Some sympathetic neurones identified electrophysiologically in the thoracic spinal cord are strongly affected by baroreceptors, chemoreceptors and respiratory afferents, suggesting they have a primary cardiovascular function (Gilbey, 1997; Janig, 2006).

Generally, these neurones display tonic activity. This could be attributed to the neurone having pacemaker-like capability. However, neither supraspinal pre-autonomic neurones (Guyunet and Stornetta, 2004) nor spinal autonomic neurones display this spontaneously (Dembowsky et al., 1985; Janig, 2006). However, many of these neurones do have intrinsic beating properties that can be enhanced by a variety of metabotropic and inotropic transmitters (Brailoiu and Dun, 2004). Therefore, like many neurones throughout the brain, it is likely autonomic neurones are conditional pacemakers, which is consistent with their dependence on multi-neurotransmitter synaptic inputs from supraspinal and suprabulbar regions (Brailoiu and Dun, 2004; Coote, 1988).

Cardiovascular-like sympathetic preganglionic neurones (Coote, 1988) have low optimum firing rates ($<10\,Hz$). Other sympathetic preganglionic neurones like those supplying the smooth muscle of the vas deferens fire at higher rates ($20\,Hz$) in bursts to facilitate the transport of sperm that accompany ejaculation in sexual activity (Stafford et al., 2006). Similarly, others that respond strongly to cutaneous afferents or gastrointestinal or urinary afferents are classified as having specific functions and patterns of activity relevant to the afferent source (De Groat, 2011; Janig, 2006).

Spinal interneurones

Further features in determining the pattern and frequency of spike discharge are the networks of interneurones, through which excitatory and inhibitory synaptic potentials become entrained to give characteristic oscillatory patterns that lead to enhanced target organ responses. It has become clear that spinal interneurones play an important role by integrating, manipulating and even generating neural activity (Deuchars, 2011). This activity may be tonic or occur in bursts each with an oscillation frequency that is dependent on the path length of the interneuronal network. Some of these interneurones are associated with the generation of rhythmic locomotor activity so enabling coupling between rhythms in motoneurones and sympathetic neurones.

The neuropil surrounding autonomic neurones is rich in amino acids, monoamines, nitric oxide and peptides or enzymes associated with their synthesis. Intracellular studies indicate that such neuroactive substances are associated with different nerve terminals and can post-synaptically modify neurone discharge. However, so far, there is no evidence to indicate organ selective function (Janig, 2006).

Spinal parasympathetic organisation

Spinal parasympathetic preganglionic neurones selectively project to rectum and colon, to bladder and to genital organs and are located separately in the grey matter of lower lumbar and sacral spinal cord (Janig, 2006). The filling and emptying functions of the urinary bladder depend on the amount of activity in stretch afferents in the bladder wall, which reflexly excites detrusor muscle to contract via pathways to the pons and midbrain from where descending axons controlling the lower urinary tract excite the detrusor muscle preganglionic neurones in the sacral spinal cord and cause relaxation of the external sphincter (De Groat, 2011). This is quite different to that which is observed in the sympathetic and parasympathetic nerves controlling erection, emission and ejaculation (Marson, 2011).

The discharge of action potentials in these neurones also suggests a dependence on networks of interneurones forming a spinal pattern generator (De Groat, 2011; Marson, 2011; Stafford et al., 2006), which is strongly affected by spinal and supraspinal afferents. The afferent terminals are chemically coded and may be inhibitory (glycine and γ-aminobutyric acid (GABA)) or excitatory (glutamate, oxytocin, galanin, dopamine and nitric oxide). Oscillatory patterns of activity are target organ selective. Distinct changes in activity occur to allow urinary bladder contraction and external sphincter relaxation when filling pressure reaches a threshold (De Groat, 2011).

The medulla organisation

Although it is now firmly established that autonomic control is exerted by the action of parallel pathways running through the

full extent of the neuraxis, the lower brainstem retains a major role in maintaining autonomic discharge and patterning these outflows in relation to both homeostatic demands and behaviour. In the context of cardiovascular control, it is responsible for the moment-by-moment regulation of sympathetic and vagal output to the heart through its control of (1) cardiac vagal preganglionic neurones and (2) premotor sympathetic neuronal discharge that also is a major source of input to sympathetic preganglionic neurones that control vascular tone. It is also at this level that the essential coupling of cardiovascular and respiratory activity is imposed to ensure respiratory homeostasis.

Brainstem parasympathetic organisation

The vagal control of the heart is exerted by preganglionic neurones that are located in the medulla oblongata. Electrophysiological studies in the 1970s (McAllen and Spyer, 1978) showed that in mammalian species, those neurones that controlled heart rate were localised within the nucleus ambiguus (NA) and had B fibre axons, while cardiac preganglionic neurones located in the dorsal vagal nucleus (DVN) controlled atrio-ventricular conduction and inotropic state (and had C-fibre axons). These latter neurones had minimal effect on heart rate. It was subsequently demonstrated that baroreceptor and chemoreceptor inputs affect selectively those preganglionic neurones localised in the NA. These neurones have a pulse-modulated discharge that is imposed synaptically by baroreceptor inputs over a relatively direct multi-synaptic pathway. They also have a marked respiratory pattern of discharge, which is phase locked with post-inspiration (Phase 1 expiration) and a variable discharge during stage 2 expiration. The pattern of discharge is imposed by a powerful inspiratory-related inhibitory input that is driven from the neighbouring respiratory pattern generator that is also located in the ventrolateral medulla. This is responsible for respiratory sinus arrhythmia, the increase in heart rate (and cardiac output) that ensures ventilation/ perfusion matching during inspiration. Similar studies have identified that the NA contains a second group of vagal preganglionic neurones. These have a distinctive inspiratory discharge, and their projections and physiological properties indicate that they are broncho-constrictor in function (Jordan, 1997).

The brainstem presympathetic organisation

In addition to the preganglionic vagal neurones, the medulla contains several groups of neurone implicated in cardiovascular control, which innervate the spinal sympathetic neuronal column (Loewy and Spyer, 1990). Of these, a group of neurones in the rostroventrolateral medulla (RVLM) are of particular importance. These have a marked cardiac rhythm in their discharge, a consequence of an inhibitory input from the arterial baroreceptors interacting with tonic excitatory input from oscillating networks of neurones in the reticular formation (Gebber, 1990). They show a tonic discharge in the absence of this input that in vivo is dependent particularly on chemoreceptor inputs, central and peripheral. Claims that these neurones are intrinsically sensitive to CO_2 levels and function as the central chemoreceptor have been disproved (Gourine et al., 2010). Astroglia on the ventral

surface of the medulla are the 'chemosensory' elements, and they in part through the release of adenosine triphosphate (ATP) and lactate, drive C1 and respiratory neurones of the ventrolateral medulla. These studies have used selective genetic engineering of neurones and glia and optogenetic activation or inhibition of neurones or glia to dissect the underlying mechanism. This role of glia in chemosensation finally resolves the question of how the CNS mediates regulation of respiration in the face of changing levels of arterial CO_2.

These observations indicate that medulla plays an essential role in cardiorespiratory control through the integration of reflex inputs and descending pathways. In the medulla, the nucleus tractus solitarii (NTS) plays a particularly important role in these interactions. First, it is the primary site of termination of sensory afferent from the visceral organs, the lungs and cardiovascular system (Spyer, 1990). The NTS is divided into several subnuclei, but these divisions have little functional significance as the neurones have extensive dendritic arborisations outside the boundaries and while afferent inputs show clear patterns of regional innervation, it is only by using electrophysiological approaches that the functional significance of this overlapping viscerotopic distribution has been revealed (Andresen and Paton, 2011; Spyer, 1990). It appears that the projection neurones of the NTS which provide connections further afield to brainstem or midbrain and forebrain are the elements with clear functional identity. There are modality-specific interactions at the initial synapse in each reflex pathway, for example, baroreceptor inputs from the carotid sinus and aortic arch may well affect the same second-order neurone. At this level or at a further stage in the NTS, inputs with similar reflex effects may converge (e.g. cardiac mechanoreceptor inputs and baroreceptor inputs). A group of baroreceptor-like NTS neurones exert an excitatory drive to NA and via GABA interneurones an inhibitory input to RVLM neurones. The principle action of a chemoreceptor input is to drive respiratory activity, which will lead to a suppression of Cardiac vagal motoneurone (CVM) discharge and tachycardia. When respiratory activity is suppressed as in the diving reflex, the direct effect of chemoreceptor activation is a vagally mediated bradycardia. This implies that there are two principle output paths from the NTS that affect CVMs; one that is an excitatory input to inspiratory neurones (and RVLM neurones) and a second that mediates baroreceptor inputs to CVMs.

The NTS has been shown using immunohistological techniques to contain neurones with a remarkable array of traditional neurotransmitters, neuromodulators and vasoactive compounds. Its intrinsic organisation suggests that there is considerable processing of inputs within the nucleus, the extent of which has been barely resolved. It is also the target for input from many if not all the descending pathways from the cortical, hypothalamic and midbrain sites that affect autonomic activity. This has been studied in some depth in the Spyer laboratory (see Spyer, 1990), after the initial observation, that activation of the hypothalamic defence area could inhibit NTS neurones receiving baroreceptor inputs and could potentially be the mechanism by which the reflex is 'blocked' during the defence reaction. This is not an all or none response but rather an ongoing modulation of reflex efficacy mediated by GABAergic interneurones within the NTS (Spyer, 1990). This control is a balance of two drives representing an effective mechanism to alter reflex efficacy in relation to the level of arousal. Conversely, the same descending pathway facilitates the

chemoreceptor reflex, so enhancing respiratory drive and arousal. It is likely that other ANS actions are similarly processed.

Hypothalamic influence

In addition to the medulla, the paraventricular nucleus (PVN) of the hypothalamus has been identified as pivotal to autonomic control (Coote, 2004; Dampney, 1994). It receives information about the status of the internal environment by means of arterial baroreceptors, chemoreceptors, atrial volume receptors as well as through blood-borne signals and central osmoreceptors located in the circumventricular organs. Much evidence confirms its importance in plasma volume control (Coote, 2004). Immunohistochemical and electrophysiological evidence supports the view that vasopressin and oxytocin peptides are located in pre-autonomic spinally projecting neurones which synapse monosynapticaly via long axons with autonomic spinal preganglionic neurones. Within the PVN local nitric oxide, neurones as well GABA neurones are potential key mechanisms for control of these pre-autonomic neurones and are involved in many other reflexes mediated via the PVN for the transfer of information within and across functionally distinct neuronal circuits (Shenton and Pyner, 2016). Associated with the connections are a variety of other neuropeptides such as orexin, neuropeptide Y (NPY), agouti-related peptide (AGRP), oxytocin, arginine vasopressin, also angiotensin, catecholamines, nitric oxide and amino acid glutamate and GABA (Coote, 2004).

Suprabulbar organisation

Focal electrical or chemical stimulation or lesions of suprabulbar regions of the brain can cause adjustments of autonomic output associated with cognitive functions, and emotion, as well as more selective actions on feeding, sex, exercise, bladder and rectal control (Taggart et al., 2016). These regions receive spinal and supraspinal afferents that form part of very long feedback loops connecting at multiple levels. In particular, some regions like the insular cortex are important to cardiac regulation in being able to modulate heart rate and rhythm, responses often accompanying emotional stress. The right anterior insular cortex is more often associated with tachycardia and pressor responses, whereas the left anterior insular more often elicits a vagal bradycardia and depressor effects. Neurones in the latter region are also excited by arterial baroreceptors, while in the former the cells are inhibited. Stimulation and recordings of neuronal activity in the insular cortex, in the cingulate gyrus, and in the basal ganglia including the amygdala show extensive feedback loops from peripheral receptors located in peripheral organs such as the gastrointestinal tract (GIT), the urinary bladder, the genitals, other viscera, the heart and vasculature, the airways, cutaneous thermoreceptors and nociceptors.

The present and future

Advances in investigative techniques have led to an increased understanding of the different roles of autonomic nerves. Such knowledge is resulting in new ways to treat disease. For example, drug-resistant hypertension can be treated by radiofrequency ablation of renal afferents; surgical removal arterial baroreceptors and surgical or pharmacological means to reduce arterial

chemoreceptor drive (DiBona and Esler, 2010; Paton et al., 2013; Prabhakar, 2016). Other examples include deep brain stimulation to aid urinary continence in patients with Parkinson's disease, surgical removal of cardiac sympathetics by removal of stellate ganglion for intractable cardiac angina, atrial or ventricular fibrillation or heart failure.

Recent studies have demonstrated that the selective optogenetic recruitment of DVN vagal discharge is able to protect left ventricular myocytes against lethal ischaemic/reperfusion injury emphasising the functional significance of the DVN control of the innervation of the myocardium (Gourine et al., 2016). Furthermore, a combination of genetic targeting and functional neuroanatomical mapping has shown that a restricted group of tonically active DVNs is responsible for the vagal-mediated negative inotropic action. Furthermore, these same neurones may exert a restraint on ventricular arrhythmic potential. Optogenetically driven silencing of these neurones led to a shortening of the ventricular effective refractory period, lowered the threshold for triggered ventricular tachycardia and elicited QT interval prolongation.

Taken together, these observations provide an interesting model of how the autonomic system is regulated and adapted to meet both homeostatic demand and behaviour. The ability to monitor ongoing, autonomic neural discharge simultaneously with end-organ activity in the context of cardiovascular activity in animal models has presented a major opportunity to establish paradigms for translational studies that will contribute to the identification of new therapies for many serious pathophysiological conditions.

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