State of the art

AMPA receptor trafficking and the mechanisms underlying synaptic plasticity and cognitive aging

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Even in healthy individuals there is an inexorable age-related decline in cognitive function. This is due, in large part, to reduced synaptic plasticity caused by changes in the molecular composition of the postsynaptic membrane. AMPA receptors (AMPARs) are glutamate-gated cation channels that mediate the overwhelming majority of fast excitatory transmission in the brain. Changes in AMPAR number and/or function are a core feature of synaptic plasticity and age-related cognitive decline. AMPARs are highly dynamic proteins that are subject to highly controlled trafficking, recycling, and/or degradation and replacement. This active regulation of AMPAR synthesis, targeting, synaptic dwell time, and degradation is fundamentally important for memory formation and storage. Further, aberrant AMPAR trafficking and consequent detrimental changes in synapses are strongly implicated in many brain diseases, which represent a vast social and economic burden. The purpose of this article is to provide an overview of the molecular and cellular AMPA receptor trafficking events that control synaptic responsiveness and plasticity, and highlight what is known currently known about how these processes change with age and disease.

Introduction

Aging is characterized by a progressive multi-systemic deterioration of biological processes that inevitably leads to death. In much of the developed world, improvements in public heath have led to significantly extended average life expectancy. In consequence, a major aim of biomedical science is to reduce or prevent the negative consequences of aging to allow individuals to remain productive, healthy, and fulfilled for as long as possible into old age.

Age-dependent decline in cognitive capacity is one of most challenging aspects of aging research. Even in otherwise healthy individuals, the ability to learn new information and to retrieve existing memory becomes compromised and limits intellectual ability. In neurodegenerative diseases such as Alzheimer's disease (AD) and other dementias, the impact on the quality of life for affected individuals, carers, and families is devastating, and these diseases constitute a huge and growing economic burden on society, with an estimated cost in 2010 in Europe of €477 billion.[1]

Surprisingly, although some studies have reported the loss of neurons between adolescence and old age,[2] this appears not to significantly contribute to age-related cognitive impairments. Rather, small, region-specific changes in neuronal morphology and structural plastic-

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Selected abbreviations and acronyms

AMPAR	*AMPA receptor*
CaMKII	*α-calcium-calmodulin-dependent protein kinase II*
ERK	*extracellular signal-related kinase*
Glu	*glutamate*
GRIP	*glutamate receptor anchoring protein*
LTD	*long-term depression*
LTP	*long-term potentiation*
MAPK	*mitogen-activated protein kinase*
NMDA	*N-methyl-D-aspartate*
PKA	*protein kinase A*
PKC	*protein kinase C*
TARP	*transmembrane AMPAR regulatory proteins*

ity such as dendritic branching and spine density appear to be much more important indicators of age-related memory decline.[3,4]

What is synaptic plasticity?

In the 1940s the Canadian neuroscientist Donald Hebb proposed that neurons strengthen their communication if the presynaptic cell persistently stimulates the postsynaptic cell. This is often restated as "*Neurons that fire together, wire together*." Applied to multiple synapses across a group of neurons, it gave rise to the concept that memories are encoded as engrams, which are biophysical changes to a neuronal network.[5] Experimental proof of experience-dependent Hebbian plasticity was first obtained in 1973 when it was shown that repeated stimulation of presynaptic perforant path cells in the hippocampus caused lasting increases in postsynaptic responses in dentate gyrus neurons in anesthetized rabbits.[6]

A diverse range of Hebbian and non-Hebbian types of plasticity have since been discovered, but can generally be divided into four main classes:

- Short-term synaptic plasticity, where activation of a synapse increases or decreases the efficacy of synaptic transmission at that particular synapse for seconds or minutes.
- Long-term synaptic plasticity, which is like short-term plasticity but where the synapse-specific changes last from minutes to a lifetime.[7]
- Metaplasticity, where synaptic or cellular activity regulates the capacity of individual synapses to undergo subsequent synaptic plasticity. This is sometimes termed the "*plasticity of synaptic plasticity*." [8]

- Homeostatic plasticity or synaptic scaling, in which a neuron adjusts sensitivity of its excitatory synapses up or down in response to network activity in order to tune synaptic gain and stabilize firing.[9]

Synaptic plasticity can either potentiate or depress synaptic function, depending on the frequency of activity at that synapse. In general, high-frequency stimulation potentiates synaptic activity, leading to long-term potentiation (LTP), whereas lower-frequency stimulation depresses synaptic activity, leading to long-term depression (LTD). A variety of presynaptic and postsynaptic factors can modulate synaptic strength but, as discussed below, it is widely accepted that synaptic plasticity is predominantly expressed through changes in the number, location, and properties of postsynaptic receptors.

Synaptic plasticity and memory

Both LTP and LTD are cellular mechanisms for learning[10,11] and there are pronounced parallels between LTP and memory formation and storage. Both have two mechanistically distinct phases, which take place on very similar time scales. The induction phase of LTP, in which synaptic function is initially enhanced, lasts under an hour. There is then a subsequent maintenance phase, in which the increased synaptic strength is fully established. In memory formation there is also an early phase, corresponding to initial learning, and a mechanistically distinguishable late phase, which corresponds to memory consolidation. The induction phase of LTP and the initial learning process in memory both occur without synthesis of new proteins, relying on post-translational modifications of proteins already present at sites of potentiation.[12] Since these changes are not permanent, and proteins have a limited half-life before they are degraded, the maintenance and consolidation phases of LTP and memory therefore both require de novo protein synthesis.[13]

Mechanisms of plasticity

The most widely studied forms of plasticity are induced by activation of postsynaptic N-methyl-D-aspartate (NMDA) receptors (NMDARs) and expressed by changes in the number of postsynaptic AMPA receptors (AMPARs).[14,15] NMDARs are nonspecific cation channels with a high permeability to Ca^{2+}. Under normal resting membrane potential, however, the channel is blocked

by Mg^{2+} ions and this block is released by membrane depolarization.[16,17] This property makes NMDARs coincidence detectors since they require both presynaptic glutamate release and postsynaptic depolarization for activation. The entry of Ca^{2+} and Na^+ ions through the activated NMDAR leads to further depolarization, and when the local intracellular Ca^{2+} concentration reaches a threshold, signal transduction pathways are initiated that ultimately lead to changes in synaptic responsiveness. Different patterns of NMDAR activity and spatiotemporal calcium dynamics elicit LTP or LTD. In electrophysiology experiments a train of electrical pulses is generally used to depolarize the neuron with high stimulus frequency to induce a rapid Ca^{2+} influx for LTP and lower frequency for LTD.[18] Strong stimulation of afferent presynaptic neurons in hippocampal slices such as trains of 4 x 100 Hz stimulation with a 200-ms interval between θ bursts causes a rapid and substantial Ca^{2+} influx at the postsynapse which initiates LTP. This is believed to resemble the physiological activity that takes place in the brain during learning processes.[19] In dispersed cultured neurons, it is possible to invoke LTP via activation of synaptic NMDARs with the coagonist, glycine.[20] In contrast, a more sustained, lower Ca^{2+} influx evoked by a high number of low-frequency stimulations, eg, 900 pulses at 0.5-5 Hz, causes LTD.[21] In addition, direct activation of NMDARs or Group I metabotropic glutamate (mGlu) receptors can cause LTD.[22,23]

AMPA receptors

AMPARs mediate the overwhelming majority of fast excitatory neurotransmission in the central nervous system (CNS) and are critically important for nearly all aspects of brain function, including learning, memory, and cognition. They are ligand-gated ion channels composed of combinations of four separate subunits (GluA1-4). AMPARs are highly mobile proteins that undergo constitutive and activity-dependent translocation to; recycling at, and removal from, synapses.[24,25] All subunits share a common membrane topology with each other, and with NMDAR and kainate receptor subunits *(Figure 1)*. Complex combinations of signaling pathways regulated by global network activity and by the history of activity at the synapse control the number, synaptic localization, and subunit composition of synaptic AMPARs. Increases in the number as well as changes in the composition and/or properties of synaptic AMPARs

mediate LTP and LTD, which occur at synapses throughout the CNS[26] *(Figure 2)*. Furthermore, as discussed below, aberrant AMPAR trafficking is implicated in neurodegenerative diseases.

AMPAR subunit composition, assembly, and ER exit

AMPARs assemble in the endoplasmic reticulum (ER) first as dimers, which then come together to form dimers of dimers to make a tetramer.[27,28] In adult rat hippocampal neurons AMPARs mainly comprise combinations of GluA1/2 or GluA2/3 subunits,[29] and synaptic AMPARs are predominantly combinations of GluA1 and GluA2.[30] The GluA2 subunit contains an RNA editing site that replaces the glutamine residue Q607 coded for in the genomic DNA to an arginine residue (Q/R editing) and almost all GluA2 is edited in adult neurons.[31] This residue forms part of the channel lining, and the switch to arginine functions both to act as an ER retention motif and to render GluA2-containing AMPARs impermeable to calcium.[32-34] GluA1, which lacks this motif, is both calcium permeable and rapidly exported from the ER and trafficked to the plasma membrane.[35] Transmembrane AMPAR regulatory proteins (TARPs) which, as discussed below, facilitate correct AMPAR folding and modify channel properties, also participate in export of AMPARs from the ER.[36]

The intracellular c-terminal domains (tails) of AMPAR subunits can be classified into either long or short tails, which determine their trafficking. GluA1 and GluA4 are long-tailed subunits but GluA4 is expressed mainly during early development and is present only at low levels in adult brain. The trafficking properties of long-tailed AMPAR subunits predominate over those of short-tailed subunits, so receptors containing the GluA1/2 subunit combination exhibit the surface trafficking properties of GluA1. They are rapidly mobilized from the receptor pool in the ER to the surface, as the GluA1 subunit masks the retention sequence in the GluA2 subunit. AMPARs comprising the short-tail subunits GluA2 and GluA3 without GluA1, are trafficked from the ER more slowly.[31,37] These receptors also constitutively recycle to and from the surface to maintain AMPAR numbers.[38] In general, GluA1 containing AMPARs are activity-dependently delivered to synapses and are then replaced by GluA2/3, leading to a net increase in synaptic AMPARs in LTP.[9-41] *(Figure 1)*.
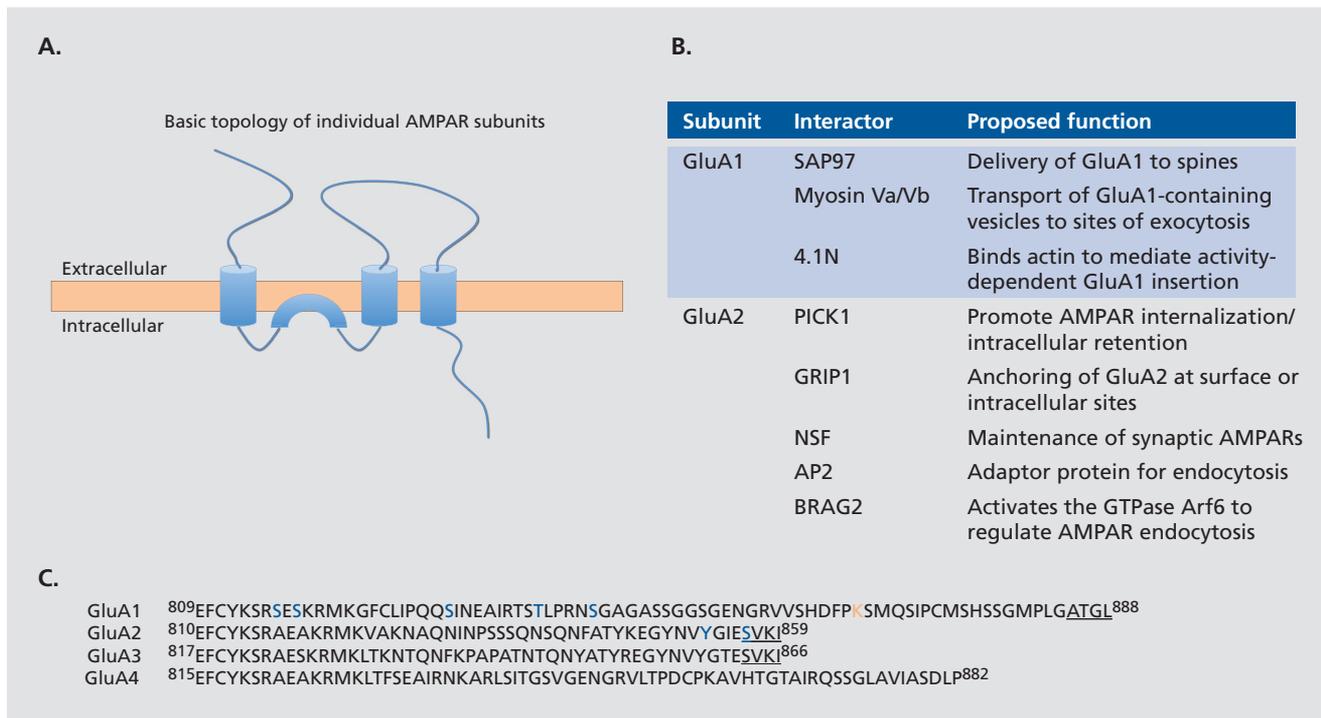
Calcium-permeable AMPARs and LTP

Q/R edited GluA2-containing AMPARs have negligible Ca^{2+} permeability.[42-44] AMPARs that either lack the GluA2 subunit or contain an unedited version (ie, Ca^{2+}-permeable AMPARs; CP-AMPARs, *Figure 3*) are initially delivered to perisynaptic sites, and are then translocated to synapses during LTP induction and subsequently replaced by GluA2-containing receptors.[45,46] The Ca^{2+} influx through GluA2-lacking AMPARs appears to drive the insertion of GluA2-containing receptors and this change from Ca^{2+}-permeable to Ca^{2+}-impermeable AMPARs stabilizes LTP.[45-47] Until this switch in AMPARs occurs the LTP status of the synapse is labile and susceptible to AMPAR removal by low-frequency stimulation. This early reversible stage in LTP likely corresponds to a fleeting experience that is never laid down as a memory.[48]

As with many other aspects of plasticity, the regulation of CP-AMPARs is regulated by phosphorylation. CP-AMPARs are incorporated into synapses via α-calcium-calmodulin-dependent protein kinase II (CaMKII)-dependent[49] and protein kinase C (PKC)-dependent[46] mechanisms during early stages of LTP and calcium influx through these receptors is required for the LTP-induced regulation of actin dynamics and spine expansion via activation of the small GTPase Rac1 and the downstream PAK-LIM kinase pathway.[50]

Protein phosphorylation in synaptic plasticity

Protein phosphorylation and dephosphorylation is an overarching regulatory mechanism of most cell signal-

A.

Basic topology of individual AMPAR subunits

Extracellular

Intracellular

B.

Subunit	Interactor	Proposed function
GluA1	SAP97	Delivery of GluA1 to spines
	Myosin Va/Vb	Transport of GluA1-containing vesicles to sites of exocytosis
	4.1N	Binds actin to mediate activity-dependent GluA1 insertion
GluA2	PICK1	Promote AMPAR internalization/intracellular retention
	GRIP1	Anchoring of GluA2 at surface or intracellular sites
	NSF	Maintenance of synaptic AMPARs
	AP2	Adaptor protein for endocytosis
	BRAG2	Activates the GTPase Arf6 to regulate AMPAR endocytosis

C.

GluA1 ^{809}EFCYKSRSESKRMKGFCLIPQQSINEAIRTSTLPRNSGAGASSGGSGENGRVVSHDFPKSMQSIPCMSHSSGMPLGATGL^{888}
GluA2 ^{810}EFCYKSRAEAKRMKVAKNAQNINPSSSQNSQNFATYKEGYNVYGIESVKI^{859}
GluA3 ^{817}EFCYKSRAESKRMKLTKNTQNFKPAPATNTQNYATYREGYNVYGTESVKI^{866}
GluA4 ^{815}EFCYKSRAEAKRMKLTFSEAIRNKARLSITGSVGENGRVLTPDCPKAVHTGTAIRQSSGLAVIASDLP^{882}

Figure 1. AMPAR subunit topology, interacting partners and diverse intracellular c-termini. A) The membrane topology of an AMPA receptor subunit (AMPAR). AMPAR subunits have large extracellular N-termini, three full transmembrane domains, and a cytoplasmic re-entrant loop, which forms the lining of the channel pore and, in GluA2, contains the RNA editing site that determines calcium permeability. The glutamate binding site is formed by the extracellular N-terminus and the loop between the second and third full transmembrane domains. The intracellular c-terminus differs between subunits and binds numerous proteins required for the trafficking and synaptic expression of AMPARs. B) Summary of GluA1 and GluA2 interacting proteins discussed in the text. See text for details. C) The intracellular c-termini of the predominant isoforms of human AMPAR subunits. Amino acid numbers represent positions in the mature protein lacking the signal peptide. Highlighted in GluA1 and GluA2 are proposed phosphorylation sites (blue) and ubiquitination sites (orange) discussed in the text. Underlined in GluA1-3 are the c-terminal PDZ ligands required for binding PDZ domain-containing proteins.

ing pathways. In neurons in general, and in plasticity in particular, the signaling pathways are especially complex involving multiple kinases and phosphatases. However, despite a wide range of kinases being implicated in LTP and LTD, the core regulatory kinases appear to be CaMKII, mitogen-activated protein kinase (MAPK), protein kinase A (PKA), and isoforms of PKC. Several comprehensive reviews have detailed the roles of AMPAR phosphorylation in plasticity.[51-54] Each of the AMPAR subunits GluA1-4 are regulated by phosphorylation. A general rule seems to be that activity-dependent phosphorylation of GluA1 delivers AMPARs to synapses in LTP, whereas GluA1 dephosphorylation is a signal for internalization and LTD. In contrast, PKC phosphorylation of GluA2 promotes internalization by releasing it from the glutamate receptor anchoring protein (GRIP) and allowing it to bind to the mobilizing protein PICK1. Thus, GluA2 phosphorylation is required

for AMPAR internalization and its dephosphorylation is important in synaptic retention.[55]

Phosphorylation and LTP

CaMKII is necessary and sufficient for LTP.[56,57] CaMKII, along with PKC, can phosphorylate the GluA1 subunit at Ser831.[58-60] Phosphorylation of Ser831 increases the conductance of homomeric GluA1 and GluA1/2 heteromers in the presence of transmembrane AMPA receptor regulatory proteins (TARPs).[61] However, the exact role of Ser831 phosphorylation in vivo is still unclear, since mice lacking phosphorylation at Ser831 still show CaMKII-dependent synaptic insertion and normal hippocampal LTP.[62,63]
CaMKII also phosphorylates the AMPAR-interacting protein stargazin. Stargazin is one of the TARPs, which are proposed auxiliary AMPAR subunits, and associates with AMPARs, delivering them to, and helping anchor them at, synapses.[64] CaMKII phosphorylation of stargazin favors its interaction with the synaptic scaffold protein PSD-95, and this interaction helps anchor AMPARs at synaptic sites.[65] Although it remains unclear how CaMKII activation drives the insertion of AMPARs during LTP, it has been reported that the molecular motor protein myosinVa is required for this effect. MyosinVa associates with AMPARs and this interaction is enhanced through activation of the small GTPase
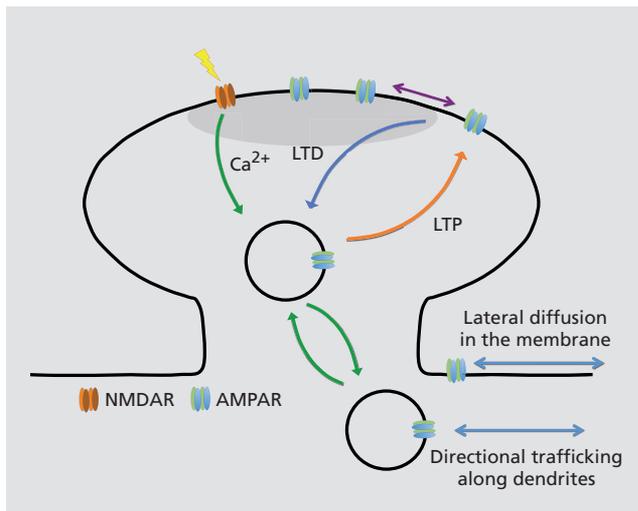
Figure 2. Basic principles of AMPAR trafficking and synaptic plasticity. Long-term changes in synaptic function can be induced by activation of postsynaptic N-methyl-D-aspartate (NMDA) receptors, which alter synaptic strength through regulating the number of postsynaptic AMPA receptors (AMPARs). NMDAR activation leads to calcium influx through the receptor, which, depending on the spatiotemporal activation profile, can initiate long-term potentiation (LTP) or long-term depression (LTD). Increased synaptic strength during LTP occurs through an increase in the number of postsynaptic AMPARs, while LTD is characterized by a decrease in postsynaptic AMPAR number. Enhanced AMPAR number during LTP can be mediated through both exocytosis of AMPARs and/or lateral diffusion of AMPARs within the membrane to the synapse. Conversely, LTD leads to AMPAR diffusion away from the synapse and receptor endocytosis.
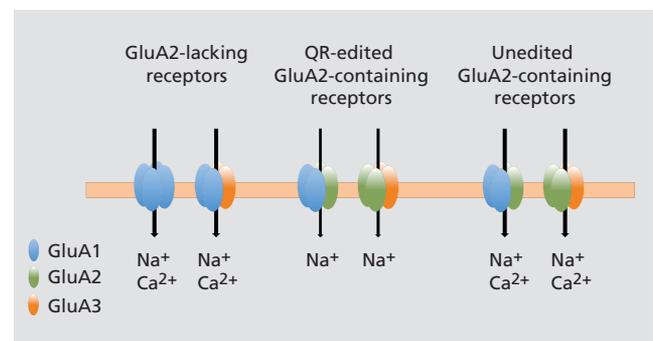
Figure 3. RNA editing of the GluA2 subunit determines calcium permeability of AMPARs. AMPA receptors (AMPARs) lacking the GluA2 subunit, or an unedited GluA2 subunit are calcium-permeable. However, receptors containing an edited GluA2 subunit do not gate calcium. For simplicity, and because their existence in neurons is unclear, GluA3 homomers, which are calcium permeable, and GluA2 homomers, whose calcium permeability depends on the RNA editing state of the GluA2 subunits involved, are not shown. GluA4 (not shown) behaves identically to GluA1.

Rab11. This mediates the short-range endosomal transport of GluA1-containing receptors from pools in the dendritic shaft, to the spine head where it can be inserted at the synapse during LTP.[66]

The role of phosphorylation in synaptic plasticity also extends beyond the synapse to enable these changes to persist in the long term. The transcription factor cAMP response element-binding protein (CREB) is important for synthesis of proteins required for LTP consolidation. CREB and other transcription factors are activated via a complex kinase cascade. Calcium entry through NMDARs during the induction stage of LTP increases levels of Ras-GTP, which activates the protein kinase Raf. Activated Raf stimulates MAPK/extracellular signal-related kinase (ERK) kinase (MEK), which activates ERK1 and ERK2, which in turn, phosphorylate the transcription factors Elk1 and CREB.[67] This leads to the synthesis of proteins required for LTP maintenance and memory consolidation.[68] The intermediate genes *Zif268* and *Arc/Arg 3.1* are upregulated by the activation of Elk1 and CREB and are specifically connected with the protein synthesis-dependent stage of memory consolidation.[69,70]

An important aspect of this Ras-ERK signaling pathway is that it is diffusive, allowing downstream effects at locations relatively distant to the initial site of activation. Furthermore, this pathway may be required to recruit AMPARs from distal sites to synapses. AMPAR exocytosis several micrometres away from potentiated synapses is prevented by blocking Ras-ERK signaling, suggesting it initiates AMPAR insertion at relatively distant dendritic regions, ready for incorporation into the synapse.[71]

The PKC family of serine/threonine kinases participate at different stages in the induction and maintenance of plasticity. LTP expression and memory formation require PKC activity[72,73] and activation of PKC can rescue LTP prevented by NMDAR blockade.[74] Direct PKC phosphorylation of Ser816 and Ser818 in GluA1 mediates activity-dependent insertion during LTP[75] by enhancing binding of GluA1 to the actin cytoskeletal linker protein, 4.1N.[76] PKC isoforms generally require both calcium and diacylglycerol for activation, although atypical PKCs (ζ and ι / λ isoforms) require neither.[77] Of these, the constitutively active atypical PKC isoform protein kinase M zeta (PKMζ) is of particular interest and has been the focus of intensive research.

PKMζ has been dubbed the "memory molecule" since it is proposed to be both necessary and sufficient to maintain potentiated synapses.[78,79] In electrophysiology experiments perfusion of PKMζ in a patch pipette has been reported to be sufficient to produce LTP in slices[78] and inhibition of PKMζ erases memory and reverses LTP in vivo.[80]

Intriguingly, inhibition of PKMζ does not block LTP induction. Rather, it prevents maintenance of LTP and can erase established memories without preventing formation of new short-term memories.[81] Subsequent studies have suggested that the mechanism of action of PKMζ appears to involve regulation of the GluA2 interacting proteins N-ethymaleimide-sensitive factor (NSF) and PICK1, although the exact mechanisms involved, and the targets of PKMζ which mediate its roles in synaptic plasticity remain unclear.[82,83] It should be noted, however that these data remain controversial since they rely mainly on the use of the zeta inhibitory peptide (ZIP) and issues have been raised about the selectivity of ZIP between different PKC isoforms.[84]

Phosphorylation and LTD

As for AMPAR exocytosis and LTP, the interplay between synaptic phosphorylation and dephosphorylation is central to regulated AMPAR endocytosis and LTD. For example, PKA is located at the postsynaptic density by the anchoring protein AKAP150, which binds directly to PSD-95. Blocking these interactions causes deficits in synaptic transmission[85] and inhibits NMDAR-dependent AMPAR endocytosis and LTD.[86] GluA1 is phosphorylated by PKA at Ser845 to regulate the open probability of the channel and promote receptor exocytosis and anchoring at perisynaptic sites.[58,87-89] Phosphorylation of Ser845, along with Ser831, appears to "prime" GluA1-containing AMPARs for LTP since, while neither residue appears absolutely required for LTP,[63] knock-in mice lacking both of these phosphorylation sites show diminished LTP[90] and mice expressing phosphomimetic aspartate residues at these positions show enhanced LTP.[91,92] However, dephosphorylation of Ser845 appears important for LTD, since mice lacking phosphorylation at this residue show defects in hippocampal LTD, potentially through phosphorylation-mediated regulation of receptor endocytosis.[63,89] Another c-terminal GluA1 residue, Thr840 is phosphorylated by PKC[93] or p70S6K.[94] Dephosphorylation at this site occurs in response to NMDA stimulation[94] suggesting a potential role in LTD.

PKC phosphorylation of GluA2 is a major determinant of LTD. Ser880 is located within the GluA2 c-terminal PDZ ligand (see below) responsible for binding to the PDZ domain-containing proteins PICK1 and GRIP. Phosphorylation of Ser880 reduces binding of GRIP1 to GluA2, but leaves PICK1 binding unaffected.[95,96] Since GRIP1 binding stabilizes GluA2 at the surface and PICK1 has been proposed to function as a mobilization factor to promote receptor internalization, this differential binding to phosphorylated GluA2 is proposed to underlie GluA2 removal during LTD.[97]

GluA2 is also phosphorylated by Src family tyrosine kinases at Tyr876, which regulates binding to the guanine-nucleotide exchange factor BRAG2. BRAG2 activates the small GTPase Arf6 and deletion of BRAG2 or inhibition of the GluA2-BRAG2 interaction prevents AMPAR endocytosis and blocks both NMDAR- and mGluR-dependent LTD.[98] Phosphorylation of GluA2 at Tyr876 reduces the GluA2-BRAG2 interaction, stabilizing GluA2-containing AMPARs at the surface.

Similarly to LTP, phosphorylation of proteins other than AMPA subunits themselves plays an important role in LTD. For example, the adaptor protein RalBP1 promotes receptor endocytosis through binding to the AP2 complex and the endocytic proteins epsin and Eps15. RalBP1 binds PSD-95 and the small GTPase RalA, which act in concert to localize RalBP1 to dendritic spines. The RalBP1-PSD-95 interaction is negatively regulated by PKA phosphorylation of RalBP1, and NMDA-induced dephosphorylation of RalBP1 by protein phosphatase 1 promotes its binding to PSD-95 to recruit RalBP1 into spines leading to AMPAR endocytosis.[99]

Multiple interacting proteins orchestrate AMPAR trafficking

AMPARs are the hub of highly dynamic macromolecular signaling complexes, which consist of a range of direct and indirect interacting proteins that regulate their biosynthesis, trafficking, scaffolding, stability, signaling, and turnover. The core components of the complex vary depending on the location of the AMPAR and the activity of the neuron.

GluA1, 2, and 3 possess a PDZ-binding motif at their extreme c-terminus *(Figure 2)*. These motifs differentially interact with proteins that contain an 80-90 amino-acid PDZ domain (PDZ is an acronym of the first letters

of three of the first proteins found to contain this domain).[100] PDZ proteins act to bind transmembrane proteins to the cytoskeleton and stabilize signaling complexes.[100]

GluA1 and GluA2 bind to different subsets of PDZ proteins. Prominent among these are GluA1 binding to synapse-associated protein 97 (SAP97)[101] and GluA2 binding to PICK1[102] and GRIP.[103]

The GluA1 interacting protein SAP97 is a member of the membrane-associated guanylate kinase (MAGUK) family of proteins that also includes PSD-95.[104] SAP97 links to microtubule-based transport mechanisms via an interaction with the motor protein myosin VI[105] and is targeted to spines by CaMKII phosphorylation to deliver GluA1 containing AMPARs.[106]

PICK1 acts as a Ca^{2+} sensor and plays important roles in both LTP and LTD. It is involved in the activity-dependent decrease in synaptic GluA2 during NMDAR-LTD[107] and contains a BAR domain that may sense existing membrane curvature, or actively induce the curvature during clathrin-coated pit formation, assisting AMPAR internalization. PICK1 also inhibits Arp2/3-mediated actin polymerization to mediate AMPAR internalization during LTD[108] and to mediate the decrease in spine size associated with LTD.[109] PICK1 shows enhanced localization with Rab5 and early endosomes on induction of NMDAR-LTP,[110] and it is involved in mediating the increase in GluA2-lacking CP-AMPARs at synapses,[111] possibly through the intracellular retention of GluA2 containing AMPARs.[112] Consistent with this, PICK1 knock-down increases the rate of AMPAR recycling to the membrane.[113]

GRIP also plays an essential role in plasticity. LTD in cerebellar Purkinje cells is abolished in GRIP knockout mice.[114] GRIP may have a role in the attachment and anchoring of AMPARs at internal[115] and/or surface locations.[116] In contrast, PICK1 mobilizes AMPARs and facilitates association with trafficking vesicles. This model explains the importance of these molecules in both forward trafficking to the synapse during LTP, and removal from the synapse during LTD. Additionally, through their interaction with GRIP, AMPARs indirectly bind the heavy chain of the motor protein kinesin[117] to direct GluA2-containing AMPARs into dendrites. GRIP also binds to the kinesin KIF1 interacting protein liprin-α[118] and to the Arf GTPase-activating protein GIT1.[119] These interactions play important roles in AMPAR distribution since inhibiting either reduces AMPAR forward traffic.

AMPAR subunit c-termini also bind to non-PDZ proteins. GluA1 binds to the Ca^{2+}-sensitive actin-based motor protein Myosin Vb[120] as well as Myosin Va.[66] Myosin Vb transports GluA1-containing AMPAR recycling endosomes to sites of exocytosis. This process couples stimuli that induce LTP to the increased trafficking of cargo necessary for AMPAR insertion and spine enlargement.[121]

GluA2 interacts directly with the ATPase NSF at a site upstream from the PDZ motif. The NSF interaction is Ca^{2+}-dependent[122] and is required for the maintenance of synaptic AMPARs.[123] Blocking NSF binding to GluA2 results in a relatively rapid rundown of AMPAR surface expression under basal non-stimulated conditions with a half-life of around 10 minutes, highlighting the dynamic nature of AMPAR surface expression and recycling.[123,124] Mechanisms include the fact that NSF binding blocks the interaction of GluA2 with the endocytic adaptor protein AP2 to prevent internalization.[125] The NSF interaction also disrupts GluA2/PICK1 binding, which prevents PICK1-mediated internalization and intracellular retention of AMPARs to promote their synaptic expression.[126]

AMPARs are regulated by auxiliary subunits

A growing number of transmembrane proteins have been proposed to associate with AMPAR complexes to function as "auxiliary subunits." What makes a protein an auxiliary subunit is a matter debate, but a tentative definition is a protein that forms a stable complex with mature AMPARs.[64] TARPs were the first defined family of AMPAR auxiliary subunits and these are critical regulators of several aspects of AMPAR trafficking, pharmacology, and channel kinetics.[64,127,128] The prototypic TARP is Stargazin (γ-2), which acts as a chaperone protein.[128,129] Stargazin mediates AMAPR exit from the ER[36,130] stabilizes synaptic AMPARs by binding to the postsynaptic density scaffolding protein PSD-95[131] via a process that involves CaMKII phosphorylation,[65] and regulates channel properties of surface expressed receptor complexes (for recent reviews on TARP function see refs 64,132).

Subsequent proteomic and homology screens have identified a number of unrelated transmembrane proteins that exhibit similar effects on AMPAR trafficking and are thus putative auxiliary subunits. Cornichon homologs-2 and -3 (CNIH-2 and CNIH-3) have been reported to increase AMPAR surface expression and markedly slow deactivation and desensitization kinetics.[133] However, later studies suggest that these proteins act as ER chaperones rather than auxiliary subunits, which associate with the mature, surface-expressed receptor complex.[134]

Cystine-knot AMPAR modulating protein (CKAMP44) is a brain-specific protein that interacts with all AMPAR subunits. It is a transmembrane protein with a cysteine-rich N-terminal domain.[135] It has a widespread distribution in brain but seems to be expressed at relatively low levels. Surprisingly, it seems that CKAMP44 reduces AMPAR currents by extending deactivation and enhancing desensitization. However, the molecular mechanisms that regulate CKAMP44 and its functional consequences on plasticity and memory remain unclear.[135]

Synapse Differentially Induced Gene 1 (SynDig1) is a transmembrane protein that regulates AMPAR localization at developing hippocampal synapses.[136] SynDig1 clusters with GluA2 in cultured neurons and coimmunoprecipitates with GluA2 when expressed in heterologous cells, and with GluA1 and GluA2 from brain extracts. Further, SynDig1 knock-down reduces synapse formation, and surface expression of both GluA1 and GluA2,[136] suggesting SynDig1 may represent a potential AMPAR auxiliary subunit with a role in synapse development. However, the relevance of SynDig1 to synaptic plasticity remains to be determined.

AMPAR surface expression and localization at synapses

AMPAR exocytosis and maintenance

The general consensus is that AMPARs are inserted into the plasma membrane close to, but not at, synapses. Once at the surface local lateral diffusion is required for constitutive cycling of AMPARs,[137] for the activity-dependent delivery of AMPARs to synapses[138] and for the replacement of desensitized AMPARs with functional nondesensitized AMPARs near the synapse to maintain synaptic transmission.[139]

During LTP induction AMPARs undergo PKA-dependent insertion at perisynaptic sites where they are initially stabilized by actin polymerization and translocate to the synapse on full expression of LTP.[48] Following membrane insertion AMPARs can either disperse

immediately, increasing the concentration of receptors available for recruitment into spines, or disperse more slowly, contributing to diffuse overall surface pools of receptors.[140] Consistent with this, most AMPARs entering spines (70% to 90%) come from receptors already expressed in adjacent areas of dendritic membrane.[141,142] One likely method of recruitment is activity-dependent dynamin-mediated endocytosis within spines, which can generate a net inward membrane drift to enhance membrane protein delivery to active spines.[143]

Even which located at the postsynaptic density AMPARs are highly dynamic and undergo constant recycling. In fact, constant cycles of exocytosis and endocytosis at zones adjacent to the PSD have been proposed to be a major mechanism for retaining AMPARs at synapses.[144] AMPARs internalize at endocytic zones (EZs) localized adjacent to the PSD. These EZs are localized through an interaction between the GTPase dynamin-3 and the adaptor protein Homer which, through its interaction with the PSD protein Shank, anchors EZs adjacent to the PSD. Paradoxically, this restricted zone of endocytosis serves to capture AMPARs as they diffuse from the PSD, allowing for them to be locally recycled, thus maintaining synaptic AMPAR number.[144] Subsequent work has suggested that localized AMPAR exocytosis occurs at a domain rich in the membrane t-SNARE syntaxin 4 close to the PSD and disruption of syntaxin 4 impairs both spine exocytosis and LTP.[145] The combination of localized endo- and exocytosis provides a highly responsive system which allows retention of synaptic AMPARs and provides a dynamic tunable mechanism through which small alterations in the ratio of insertion to internalization can profoundly alter the efficacy of synaptic transmission.

Cell adhesion molecules contribute to anchoring AMPARs at synapses

Trans-synaptic cell adhesion molecules play important roles in the synaptic localization of AMPARs during plasticity.[146] N-cadherin is a member of the cadherin family of proteins that mediate Ca^{2+}-dependent adhesion.[147] Cadherins rapidly accumulate at points of cell-cell contact prior to synaptic differentiation and disruption of cadherin-based contact inhibits the formation of synapses in primary hippocampal cultures.[148] N-cadherin increases surface expression of GluA1[149] and a protein complex of N-cadherin, δ-catenin, ABP and GRIP

retains GluA2/3 at synapses.[150] Additionally, N-cadherin appears to interact with the extracellular N-terminal domain of GluA2 and disruption of this interaction prevents GluA2-mediated spine enlargement.[151]

Neurexins and neuroligins are another class of trans-synaptic cell-adhesion molecules that play important roles in synapse formation, signaling across the synapse and synaptic function.[152] Neuroligin aggregations cluster postsynaptic proteins including GluA2-containing AMPARs[153] and disrupting neurexin-neuroligin interactions prevents AMPAR accumulation at synapses.[154] Thus, in addition to their structural roles, synaptic adhesion molecules serve to restrict the mobility of AMPARs to regulate synaptic maturation and strength.

AMPAR post-endocytic sorting, degradation pathways, and synaptic plasticity

The sorting events that occur following endocytosis and the regulation of protein degradation are critical aspects of AMPAR trafficking. AMPARs can either be recycled back to the plasma membrane or sorted for lysosomal degradation.[155,156] However, the pathways determining whether AMPARs are recycled or degraded have remained elusive. In fact, as outlined below, AMPARs can be degraded by both the ubiquitin-proteasome and ubiquitin-lysosome systems, both of which are strongly implicated in age-related neurodegenerative diseases.

The turnover of many proteins is regulated post-translational modification with the protein ubiquitin. Ubiquitin is conjugated to lysine residues in target proteins through the sequential action of E1, E2, and E3 enzymes. Ubiquitin can target a single lysine in a substrate protein (monoubiquitination) or, through internal lysine residues within ubiquitin itself, form chains (polyubiquitination), leading to distinct trafficking and degradative pathways.[157] It is well established that ubiquitin mediated protein degradation plays a central role in synaptic function and plasticity.[158] For example, NMDAR activation can recruit proteasomes to spines and regulate proteasomal function.[159] Inhibition or dysfunction of Na^+/K^+ ATPase causes a rapid decrease in surface expressed and total AMPARs by turnover through proteasome-mediated proteolysis.[160] PSD-95 is ubiquitinated in response to NMDAR activation and rapidly degraded by the proteasome. Proteasome inhibitors or mutations that block PSD-95 ubiquitination prevent NMDA-induced AMPAR endocytosis and LTD.[161]

AMPAR subunits have been reported to be directly ubiquitinated.[162-165] Agonist activation induces the Ca^{2+}-sensitive ubiquitination of GluA1 by the E3 ligase Nedd4-1, which specifically binds GluA1, leading to endocytosis and lysosomal degradation.[162,164] Ubiquitination occurs primarily at Lys868 and overexpression of Nedd4 enhances GluA1 ubiquitination and decreases AMPAR surface expression.[162,164] Knock-down of Nedd4 reduces GluA1 ubiquitination and blocks agonist-induced endocytosis of GluA1-containing AMPARs.[164] Interestingly, GluA1 ubiquitination is specific to agonist stimulation since AMPARs internalized in response to NMDAR activation were not ubiquitinated.[162]

GluA1 has also been reported to be ubiquitinated in response to EphA4 activation during homeostatic plasticity.[166,167] Cdh1, a component of the multi-protein ubiquitin ligase anaphase-promoting complex (APC) binds to and ubiquitinates GluA1 leading to degradation via the ubiquitin/proteasome system.[166] Thus, depending on the stimulus and the ligase involved, ubiquitin modification of GluA1 can lead to either endocytosis followed by lysosomal degradation or to degradation by the proteasome.

It has also been reported that GluA2 can be directly and rapidly ubiquitinated in response agonist stimulation or by increasing synaptic activity by antagonizing $GABA_A$Rs with bicuculline.[163] As for GluA1, NMDAR activation does not cause GluA2 ubiquitination but, in contrast to GluA1, clathrin and dynamin activity is required for GluA2 ubiquitination suggesting modification occurs after endocytosis.[163] Since the currently defined E3s for AMPAR ubiquitination appear to be GluA1-specific, it will now be important to define the E3s involved in GluA2 ubiquitination and the effects on AMPAR stability, localization and function.

Homeostatic scaling and AMPAR trafficking

Homeostatic scaling is a negative feedback process by which neuronal excitability is adjusted to compensate for changes in network activity.[168] Chronically reducing neuronal activity by, for example, preventing action potentials using the sodium channel blocker teterodotoxin (TTX) or blocking NMDA or AMPAR receptors enhances synaptic strength. Conversely, chronic increases in neuronal activity reduce synaptic strength. These homeostatic feedback mechanisms tune neuronal excitability and maintain network activity within a physiologically tractable range. At the postsynaptic membrane homeostatic synaptic scaling is mediated by altering the number of synaptic AMPARs. Many of the trafficking pathways outlined above have been implicated in scaling evoked AMPAR insertion or removal. Importantly, scaling processes are highly relevant to aging and one emerging concept is that inappropriate scaling contributes to the progression of Alzheimer's disease.[169]

The increase in AMPARs evoked by sustained suppression of synaptic activity exhibits some properties in common with AMPAR increases during LTP. There is an initial insertion of Ca^{2+}-permeable AMPARs and subsequent replacement with GluA2-containing Ca^{2+}-impermeable AMPARs.[170-173] This initial insertion of GluA1 may signal the recruitment of GluA2 containing receptors since inhibitors of CP-AMPARs block scaling at early, but not at later, timepoints.[174] However, some studies have reported the recruitment of both GluA1 and GluA2 in response to suppression of neuronal activity[175,176] and GluA2 has been reported to be required for initial synaptic scaling,[177] suggesting that the mode of induction of homeostatic scaling, as well as the neuron and synapse type, may determine the AMPAR subunit specificity required.

Various secreted molecules are important for synaptic scaling. Glial cell-derived TNFα increases surface GluA1 followed at later time points by GluA2.[178-180] Brain-derived neurotrophic factor (BDNF) has differential effects on synaptic scaling depending on the synapse.[181,182] Similar to TNFα, BDNF-mediated scaling leads to an initial enhancement of GluA1 surface expression followed by increased GluA2 at later timepoints.[183,184] Decreased synaptic activity also increases retinoic acid synthesis and enhances synaptic transmission via increased translation and surface delivery of GluA1 containing AMPARs.[172] As with Hebbian plasticity, a complex interplay of kinases and phosphatises contribute to both homeostatic scaling with documented roles for several CaMKII isoforms.[185-187]

Cell adhesion molecules contribute to the synaptic retention of AMPARs in homeostatic plasticity. Dominant negative N-cadherin reduces TTX-induced upscaling[188] and decreased network activity increases surface levels of postsynaptic β-3-integrin, which stabilizes synaptic AMPARs by decreasing GluA2 endocytosis through activation of the GTPase Rap1.[189]

Homeostatic scaling requires protein synthesis and Arc/Arg3.1 undergoes activity-dependent translation induced by neuronal activity.[9,190] Overexpression or knockdown of Arc respectively up or down regulates basal AMPAR endocytosis via pathways in which Arc interacts with endophilin and dynamin components of the endocytic machinery.[191] In vivo levels of Arc control spine density and morphology, and specifically regulate AMPAR trafficking at thin spines.[192] As expected of a protein that so intimately controls surface AMPAR number, Arc is also subject to tight post-translational regulation and is modified by both ubiquitin[193] and SUMO,[194] which act to regulate Arc number and activity, respectively, in order to tune synaptic AMPAR number to neuronal activity.

Synaptic plasticity in normal aging

Cognitive decline, such as mild defects in working or special memory, is an unavoidable consequence of aging. However, while numerous neurodegenerative disorders are characterized by dramatic neuronal cell death, this does not seem to be a characteristic of normal age-related cognitive decline. Rather, it appears that age-related cognitive decline is mediated through alterations in synaptic number and function in brain regions responsible for memory-related tasks, such as the hippocampus or prefrontal cortex (for reviews see refs 4, 195).

To our knowledge, no studies have directly assessed the trafficking of AMPARs in animal models of normal aging, but the capacity of hippocampal synapses to exhibit plasticity has been investigated. Although the biophysical properties of hippocampal granule or pyramidal neurons seem to be largely unaffected in aging animals,[196] depending on the hippocampal synapse examined, aged animals show either a higher threshold for LTP induction[197] or a decreased level of LTP induction compared with young animals.[198-200] In addition, LTP maintenance is decreased in the dentate gyrus and CA3 of aged rats,[201,202] and LTP observed in these animals is more susceptible to depotentiation.[203] Thus, while aged animals still exhibit LTP, higher levels of stimulation are required and the potentiation is less stable. Conversely, aged animals show enhanced induction of LTD at CA3-CA1 synapses, potentially as a result of differences between calcium homeostasis between young and old rats.[203]

Thus, it seems clear that deficiencies in synaptic plasticity occur during normal aging and these deficits are likely attributable to defects in AMPAR trafficking.

AMPAR trafficking and neural disease

Essentially all age-associated neurological and neurodegenerative disorders involve synaptic abnormalities. A particularly well-studied example of AMPAR dysfunction in disease pathogenesis is Alzheimer's disease (AD). Multiple approaches have been used to model the pathology of AD and common general features of these models are reduced synaptic AMPARs and aberrations in LTP[204] and LTD.[204,205] Furthermore, disruption of AMPAR trafficking by soluble amyloid beta (Aβ) oligomers is a major causative agent of synaptic dysfunction in AD.[206]

Aβ treatment of neurons leads to decreased AMPAR surface expression through increased AMPAR endocytosis.[207] Interestingly, there are functional similarities between LTD and Aβ-induced AMPAR internalization,[208] suggesting these processes may occur through common mechanisms. Synaptic localization of CaMKII is altered in APP transgenic mice and in cultures treated with Aβ oligomers. Knockdown of CaMKII occludes, and CaMKII overexpression blocks the effect of long-term exposure to Aβ on AMPAR surface expression.[209] LTD and the Aβ-induced loss of synaptic AMPARs also share other signaling molecules including p38, MAPK, calcineurin (PP2B), and GSK3β.[205] Inhibition of calcineurin-mediated AMPAR endocytosis prevents Aβ induced AMPAR internalization and spine loss.[207] Similarly, GSK3 inhibition prevents Aβ effects on steady state AMPAR surface expression and delivery of AMPAR into spines following LTP.[210]

Another route that Aβ interferes AMPAR trafficking appears to be competition with proteolytic maturation of BDNF, which is required for synaptic potentiation associated with classical conditioning.[211] The only direct binding partner reported for Aβ oligomers to date is the cellular prion protein (PrP[C]),[212] but this accounts for only half of the total oligomer binding. Intriguingly, however, Aβ oligomers preferentially label GluA2-positive spines and crosslinking experiments suggest that the Aβ oligomers bind in close proximity to GluA2-containing complexes.[207] Furthermore, AMPAR antagonists inhibit Aβ oligomer binding and synaptic loss, raising the possibility that Aβ may affect AMPAR trafficking by binding directly to the GluA2 protein complex.

Concluding remarks and future directions

In the last 20 years there has been remarkable progress in the field of AMPAR trafficking. We now understand

in increasing molecular detail how AMPARs are inserted into and removed from the plasma membrane, as well as how they diffuse within the membrane to and from the synapses. Impressive though these advances are, much more work is needed before it will be possible to envisage therapeutic strategies for correcting defects in higher brain function associated with aging. For example, it is unclear how memories encoded by synaptic plasticity and network engrams are retained over a lifetime when the synaptic AMPARs that provide the substrate for this information storage have a half-life of about 30 hours. Framed in this way, the surprising fact is that any memories are retained in old age, rather than that there is age-related memory decline. However, recent work has begun to examine the differences in memory formation and synaptic plasticity in various animal models of both normal aging and of neurodegenerative disease. A crucial aspect of future research will therefore involve extending these observations and relating them to what we already know about the trafficking and behaviour of AMPA receptors. Fundamentally, we must seek to define the molecular pathways of AMPAR trafficking that underlie the defects in synaptic plasticity and memory formation associated with cognitive aging and neurodegenerative disease. The challenge of this transition from the observed defects to the unpicking of the molecular detail is not to be underestimated. However, defining the underlying molecular and cellular mechanisms of age-dependent alterations in AMPAR trafficking and defining the functional consequences for synaptic transmission represent key long-term goals that hold promise for the development of strategies to combat the memory loss associated with both normal aging and age-related neurological disorders. ❏

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El transporte del receptor AMPA y los mecanismos subyacentes a la plasticidad sináptica y el envejecimiento cognitivo

Incluso en los sujetos sanos existe una inexorable declinación de la función cognitiva relacionada con la edad. Esta es debida, en gran parte, a una reducción de la plasticidad sináptica causada por cambios en la composición molecular de la membrana postsináptica. Los receptores AMPA (AMPARs) son canales catiónicos dependientes de glutamato que median la mayor parte de la transmisión excitatoria rápida en el cerebro. Los cambios en el número y/o función de los receptores AMPAR constituyen una característica central de la plasticidad sináptica y de la declinación cognitiva relacionada con la edad. Los AMPARs son proteínas altamente dinámicas que están sujetas a un alto control respecto al transporte, reciclado y/o degradación y reemplazo. Esta regulación activa de la síntesis, localización, tiempo de permanencia en la sinapsis y degradación de AMPAR es de fundamental importancia para la formación y almacenamiento de la memoria. Además, el transporte aberrante de AMPAR y los consecuentes cambios dañinos en las sinapsis se asocian fuertemente con muchas enfermedades cerebrales, las que representan un gran costo social y económico. El propósito de este artículo es aportar una perspectiva de los acontecimientos moleculares y celulares del transporte del receptor AMPA que controlan la respuesta sináptica y la plasticidad, y destacar lo que actualmente se sabe acerca de cómo estos procesos cambian con la edad y la enfermedad.

Circulation du récepteur AMPA et mécanismes sous-tendant la plasticité synaptique et le vieillissement cognitif

Le déclin cognitif lié à l'âge, inexorable même chez les individus sains, est dû en grande partie à une diminution de la plasticité synaptique causée par des changements de la composition moléculaire de la membrane post-synaptique. Les récepteurs AMPA (AMPAR) sont des canaux de cations contrôlés par le glutamate qui assurent la médiation de la grande majorité de l'excitation rapide du cerveau. Les modifications en nombre et/ou en fonction des AMPAR sont au cœur de la plasticité synaptique et du déclin cognitif lié à l'âge. Les AMPAR sont des protéines extrêmement dynamiques sujettes à une circulation, un recyclage et/ou une dégradation et à une substitution très contrôlés. Cette régulation active de la synthèse, du ciblage, du temps de maintien synaptique et de la dégradation des AMPAR est fondamentalement importante pour le stockage et la formation de la mémoire. De plus, une circulation aberrante des AMPAR et les modifications préjudiciables qui s'en suivent dans les synapses sont fortement impliquées dans de nombreuses maladies cérébrales, ce qui représente un lourd fardeau économique et social. Cet article a pour but de présenter la circulation du récepteur moléculaire et cellulaire AMPA qui contrôle la plasticité et la réactivité synaptiques et de souligner les connaissances actuelles sur les changements de ces processus avec l'âge et la maladie.

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