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Regulation of AMPA Receptor Activity, Synaptic Targeting and Recycling: Role in Synaptic Plasticity*

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The alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors for the neurotransmitter glutamate are oligomeric structures responsible for most fast excitatory responses in the central nervous system. The activity of AMPA receptors can be directly regulated by protein phosphorylation, which may also affect the interaction with intracellular proteins and, consequently, their recycling and localization to defined postsynaptic sites. This review focuses on recent advances in understanding the dynamic regulation of AMPA receptors, on a short- and long-term basis, and its implications in synaptic plasticity.

KEY WORDS: Glutamate receptors; AMPA receptors; synaptic plasticity; protein phosphorylation; endocytosis; synaptic targeting.

INTRODUCTION

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS). Glutamate is the agonist of two distinct categories of glutamate receptors, metabotropic glutamate receptors and ionotropic glutamate receptors. Ionotropic glutamate receptors have been divided in three classes, according to their pharmacological, molecular, and electrophysiological properties: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors (1,2). Binding of synaptically released glutamate to ionotropic glutamate receptors produces a depolarization of the postsynaptic region. Each class of receptors plays different roles in synaptic transmission. AMPA receptors mediate the rapid excitatory synaptic transmission (2), whereas kainate receptors regulate neuronal activity predominantly at a presynaptic level (3). NMDA receptors mediate a slower component of excitatory neurotransmission and are blocked by magnesium at resting potential. NMDA receptor activation and subsequent calcium influx are crucial in the induction of specific forms of synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD) (2,4). In this review we focus on recent advances in the regulation of AMPA receptors and their role in synaptic plasticity.

AMPA receptors are tetrameric structures that combine homologous subunits GluR1 to GluR4 (or GluRA to GluRD) in different stoichiometries to form receptors with distinct properties (1,5). Each monomer carries its own glutamate binding site and contributes with a specific membrane-inserted hydrophobic amino acid sequence to form the cation permeable channel (TM2 region). Besides this hydrophobic sequence, each subunit has three transmembrane segments (TM1, TM3,

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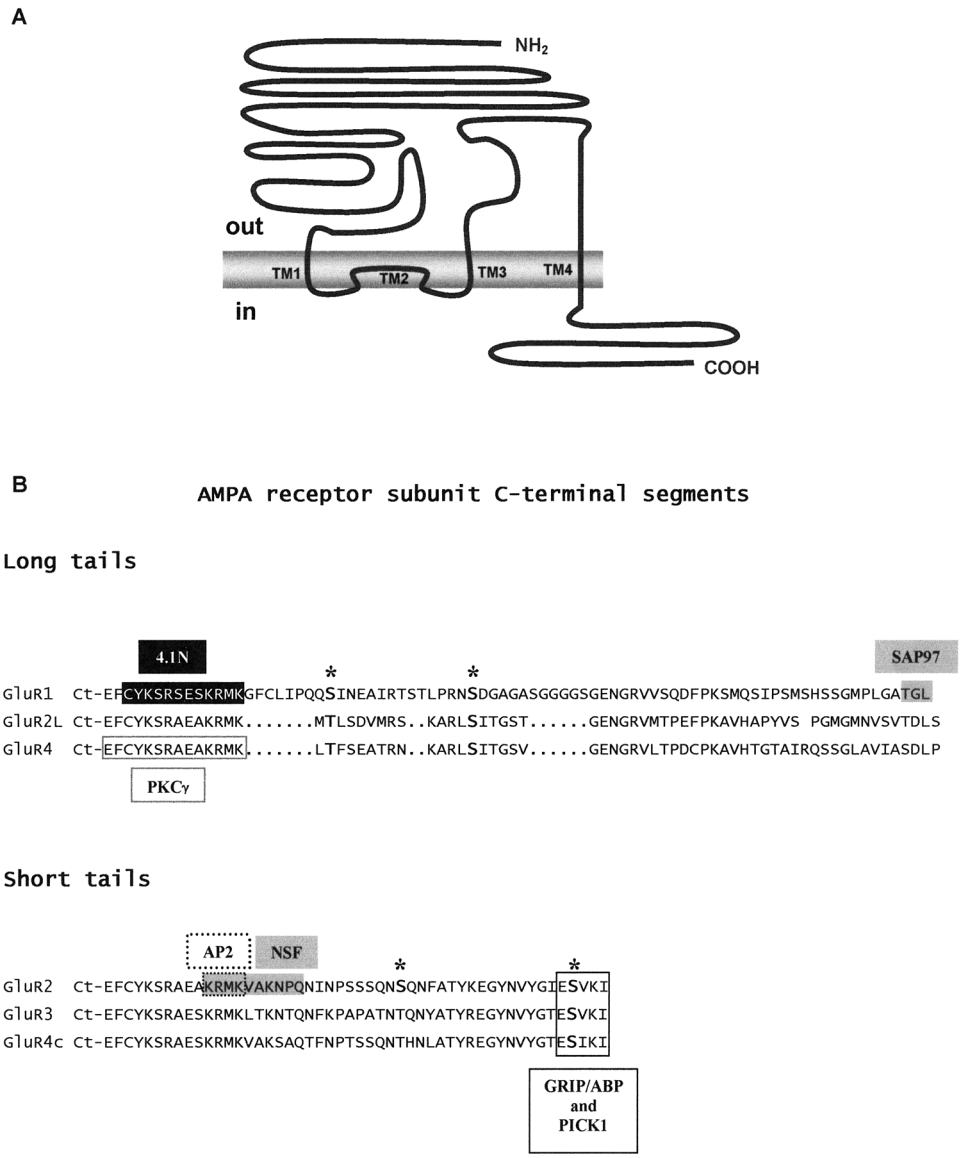

Fig. 1. Schematic representation of the topology of an AMPA receptor subunit (A). Sequence alignment of the intracellular C-terminal segments of long-tailed (GluR1, GluR2L, and GluR4) and short-tailed (GluR2, GluR3, and GluR4c) AMPA receptor subunits. Protein binding sites on AMPA receptor (box) and S/T phosphorylation sites are indicated (bold and *) (B).

and TM4) arranged in such a way that the N-terminal domain of the receptor subunits is extracellular and the C-terminal segment is intracellular (Fig. 1A). AMPA receptor subunits are homologous in their extracellular and transmembrane regions, but are distinct in their intracellular cytoplasmic C-terminal tails, which interact with intracellular proteins, and where the phosphorylation sites reside. GluR1, GluR4, and a splice variant of GluR2 (GluR2L) have long cytoplasmic C-terminal tails, whereas GluR2, GluR3, and the alternative splice form of GluR4 (GluR4c) have shorter cytoplasmic domains (Fig. 1B). There is homology among long forms as well as among short forms of AMPA receptor subunits. In the adult hippocampus, receptors made of GluR1/GluR2 and of GluR3/GluR2 predominate (6), whereas GluR4 is present in the immature hippocampus (7), as well as in other mature brain regions, such as the thalamus and the cerebellum (8,9). Receptors composed of subunits with short cytoplasmic C-termini (GluR2/3) cycle continuously in and out of the synapse, whereas

receptors that contain subunits with long cytoplasmic C-termini (GluR1/2 and GluR2/4) are delivered to synapses upon synaptic activity (7,10,11).

AMPA Receptor Phosphorylation

Phosphorylation of ligand-gated ion channels is crucial in the regulation of their function and plays an important role in the mechanisms of synaptic plasticity (12). In what concerns AMPA receptors, initial studies demonstrated the importance of protein kinase activity in their regulation. In these studies protein kinase activity in neurons was manipulated using appropriate drugs (for a review see [13]), by intracellular perfusion with inhibitor peptides (14), or with constitutively active kinases (15,16). Later, biochemical analysis of AMPA receptor phosphorylation found evidence for the direct phosphorylation of AMPA receptor subunits by intracellular kinases and identified several phosphorylation sites on AMPA receptor subunits (see below). The functional relevance of the phosphorylation of these sites is beginning to emerge: phosphorylation of AMPA receptor subunits changes their activity, but also affects their interaction with intracellular proteins and their surface expression and synaptic targeting (Table I).

GluR1 AMPA receptor subunit is phosphorylated at its C-terminal domain in Ser831 by protein kinase C (PKC) and Ca^{2+}-calmodulin–dependent protein kinase (CaMKII) (17,18), and in Ser845 by cyclic AMP-dependent protein kinase (PKA) (19). Phosphorylation of Ser845 by PKA underlies the potentiatory effect of PKA on GluR1 currents in transfected human embryonic kidney (HEK) 293 cells, because the effect is not observed for a Ser845 mutant (19). Further work demonstrated that PKA phosphorylation of Ser845 regulates the open channel probability of AMPA receptors (20). Perfusion of cells expressing GluR1 with CaMKII also resulted in a potentiatory effect on GluR1 currents, and a Ser831 to alanine mutant of GluR1 failed to be potentiated by the perfused kinase (18). Later work showed that CaMKII phosphorylation of Ser831 in GluR1 increases the single channel conductance of AMPA receptors (21). Phospho specific antibodies against the GluR1 phosphorylation sites have proven instrumental in studying GluR1 phosphorylation *in vivo* and in demonstrating that GluR1 phosphorylation changes during LTP and LTD (see Section "Role of MMPA Receptor Phosphorylation and Trafficking in Synaptic Plasticity" modulation of AMPA receptors in LTD). On the other hand, phosphorylation of GluR1 has been shown to regulate GluR1 incorporation in synapses. CaMKII drives the synaptic incorporation of GluR1-containing AMPA receptors (10), and PKA phosphorylation of Ser845 in GluR1 is a requisite for synaptic incorporation of GluR1 mediated by CaMKII (22).

The GluR4 AMPA receptor subunit is phosphorylated at Ser842 within its C-terminal, both *in vitro* and *in vivo* (23). PKA, PKC, and CaMKII can phosphorylate this site in GluR4. Thr830 in GluR4 is also phosphorylated by PKC *in vitro* (23). Early in the postnatal development of the hippocampus, AMPA receptors containing the GluR4 subunit are delivered to synapses in an activity-dependent manner that requires PKA activity (7). It has recently been found that activity-driven PKA phosphorylation of GluR4 in Ser842 is necessary and sufficient to relieve a retention

Table I. Functional Effect of AMPA Receptor Phosphorylation

AMPA receptor subunit	Phosphorylation site	Kinases	Functional effect
GluR1	Ser831	PKC (17) CaMKII (17,18)	• ↑ Open channel conductance of the receptor (21) • Drives synaptic incorporation of receptors (10)
	Ser845	PKA (19)	• ↑ Apparent open-channel probability of the receptor (20) • Necessary for synaptic incorporation of receptors (22) • Essential for efficient LTP (22)
GluR2	Ser880	PKC (26,27)	• Regulates interaction of GluR2 with GRIP and PICK1 (26,27) • Drives GluR2 internalization (28)
	Ser863	PKC (25)	• Unknown
GluR4	Thr830	PKC (23)	• Unknown
	Ser842	PKA (23) PKC (23) CaMKII (23)	• PKA phosphorylation relieves retention signal in GluR4 (22)

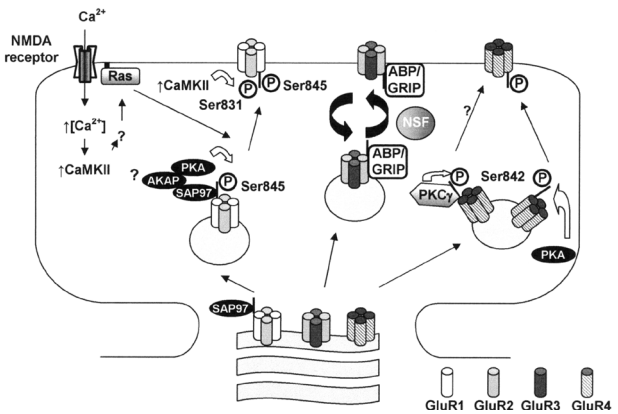

Fig. 2. Regulation of intracellular traffic of AMPA receptor subunits. Progression of GluR1 along the early secretory pathway is possibly driven by interaction with SAP97, which binds to the receptor subunit while it is still in the ER. SAP97 also binds AKAP79/150, which may link GluR1 to PKA, and phosphorylation of GluR1 at Ser845 by PKA is required for receptor incorporation in the membrane. CaMKII activity is also required to trigger the machinery leading to synaptic incorporation of the receptors, involving a mechanism mediated by Ras signaling. GluR2 subunits are sequestered in the ER by a mechanism involving the participation of the Q/R-editing site in the channel-lining pore, and the PDZ domain of this type of subunit is involved in the ER exit. In contrast with GluR1, GluR2 subunits are thought to traffic continuously to maintain the homeostasis of AMPA receptors at the membrane, and during trafficking they may associate with intracellular and plasma membrane sites via ABP/GRIP. PKA phosphorylation of GluR4 (at Ser842), which is expressed early during postnatal development, is sufficient to induce synaptic incorporation. PKCγ bound to GluR4 may also phosphorylate GluR4 at Ser842.

interaction and to drive GluR4-containing receptors into synapses (22). Moreover, GluR4 was shown to directly interact with protein kinase C gamma (PKCγ) through a C-terminal membrane proximal region, and PKCγ bound to GluR4 preferentially phosphorylates GluR4 in Ser842 ([24] Fig. 2; see Section "Non-PDZ domain–containing proteins").

The GluR2 subunit is also phosphorylated on its C-terminal domain, at Ser863 (25) and Ser880 (25–27), phosphorylation sites that are conserved in the other short AMPA receptor subunits (GluR3 and GluR4c). Moreover, Ser880 is part of the PDZ (PSD-95, Disc Large, and Z0-1) domain-binding motif at the extreme C-terminus of the short AMPA receptor subunits. PKC phosphorylates Ser880 both *in vitro* and *in vivo*, and phosphorylation of Ser880 interferes with the binding of GluR2 to PDZ-domain–containing proteins such as GRIP (glutamate receptor interacting protein) and PICK-1 (protein interacting with C kinase) (26,27). Interestingly, phosphorylated GluR2 can bind PICK-1 but not GRIP and is rapidly internalized (28). Phosphorylation of GluR2 plays a role in the differential binding of GluR2 to interacting PDZ domain–containing proteins and is a critical means to regulate receptor trafficking (see Section "PDZ domain–containing proteins").

Proteins Interacting with AMPA Receptors

AMPA receptor localization at the postsynaptic membrane of excitatory synapses is dynamically regulated. Targeting of receptors to synapses is thought to be mediated through interaction of the C-termini of AMPA receptor subunits with scaffolding proteins (reviewed in [29]). The AMPA receptor–interacting proteins include PDZ domain–containing proteins, such as GRIP/ABP (glutamate receptor–interacting protein/AMPA binding protein), PICK1, syntenin, and SAP97 (synapse-associated protein), and proteins lacking a PDZ domain, such as stargazin, Lyn tyrosine kinase, neuronal activity-regulated pentraxin (Narp), *N*-ethylmaleimide-sensitive fusion protein (NSF), and PKCγ. A summary of AMPA receptor interacting proteins and their functions is shown in Table II.

PDZ Domain–Containing Proteins. The GRIP/ABP group of proteins includes GRIP1, GRIP2, ABP-L, and ABP-S, characterized by the presence of seven (GRIP1, GRIP2, and ABP-L) or six (ABP-S) PDZ domains. GRIP/ABP binds to the C-terminal consensus sequence ES(V/I)KI of GluR2/3 or 4c AMPA receptor subunits through their PDZ motif (PDZ4 and 5 for GRIP and PDZ3, 5, and 6 for ABP [30–32]). Recently it was reported that GRIP can weakly interact with the C-terminal segment of GluR4 (33).

GRIP is localized at synapses but also in post-Golgi vesicles, suggesting that GRIP may be involved in AMPA receptor traffic to dendrites. GluR2 C-terminal PDZ-binding motif was determined to be necessary for time-dependent surface accumulation of GluR2 receptors at the synaptic surface, but seems not to be important for synaptic targeting of the receptors. It is proposed that the interaction of GRIP/ABP with GluR4 plays a role in receptor stabilization. Mutation of the PDZ-binding motif (ESVKI) on GluR2 to EAVKI blocks GluR2 interaction with GRIP/ABP and decreases AMPA receptor accumulation, but does not affect PICK1 binding to GluR2, indicating that PICK1 is not involved in receptor surface accumulation. It was also demonstrated that GluR2, when phosphorylated at Ser880 by PKC, is not able to bind GRIP, but still binds PICK1. PICK1 and GRIP bind to the same segment of GluR2; thus phosphorylation of GluR2 may function as a signal to recruit PICK1 to the receptor complexes (26,34). More recently it was

Table II. AMPA Receptor–Interacting Proteins and Their Functions

AMPAR-interacting protein	AMPAR-interacting Subunit	Function
GRIP/ABP	GluR2/3, GluR4c, GluR4 (30,33)	• Membrane surface and intracellular receptor stabilization (30,35,36)
PICK1	GluR2/3, GluR4c, GluR4 (33,37,39)	• Receptor clustering (39) NMDA-induced AMPA receptor downregulation (40) • AMPA receptor internalization (28,40)
SAP97	GluR1 (41)	• Recruitment of protein kinases and phosphatases through AKAP (42,43) • Trafficking along the early secretory pathway (44) • May be necessary for CamKII to drive synaptic delivery of GluR1 (10)
Syntenin	GluR1, GluR2, GluR4, GluR2c, GluR3c (33)	• Unknown
Lyn	GluR1, GluR2/3, GluR4c (47)	• Activation of MAPK pathway upon AMPA receptor stimulation (47)
Narp	GluR1-3 (48)	• Receptor clustering and excitatory synapse formation (48)
Stargazin	GluR1, GluR2, GluR4 (49)	• Targeting receptors to the membrane surface (49)
NSF	GluR2 (51,52)	• Targeting receptors to the membrane surface (35,53)
AP2	GluR2 (56)	• NMDA-induced AMPA receptor internalization (56)
4.1N	GluR1 (57)	• Surface receptor stabilization (57)
PKCγ	GluR4 (24)	• Facilitates receptor phosphorylation (24)

suggested that GRIP/ABP binding to GluR2 is necessary to stabilize an intracellular pool of receptors that have been internalized upon AMPA stimulation (35). Also, a new splice variant of ABP-L, containing a unique 18–amino-acid N-terminal sequence that can be palmitoylated, was characterized (pABP-L [36]). ABP-L is abundant in the cell body of cultured hippocampal neurons, but is also found in dendritic shafts, and co-localizes with the internal pools of GluR2 receptors, whereas pABP-L associates with the cell membrane, mainly in spine structures, where it colocalizes with surface GluR2. This suggests that differential palmitoylation enables ABP to play a dual role in the trafficking of receptors, serving as an anchor that stabilizes receptors either at the synapse or at intracellular locations (36).

PICK1 possesses a unique PDZ domain responsible for its association with GluR2, GluR3, or GluR4c AMPA receptor subunits (37), and a weak interaction of PICK1 to the C-terminal segment of GluR4 was recently reported (33). PICK1 was first described to interact with the catalytic domain of protein kinase C alpha (PKCα) (38), and it is a substrate for the C kinase. However, the interaction between the two proteins is independent of the PICK1 phosphorylation state. Mutation of the PDZ amino acids L27A and D28A eliminates PICK1-PKCα interaction, and the mutation L27G abolishes PICK1 association with GluR2, indicating that the same PICK1 domain interacts with both PKC and GluR2 (37). PICK1 can homo-oligomerize through its PDZ domain at a site different from the PKCα binding site, allowing the cross-linking of GluR2/3 to PKCα. Accordingly, PICK1 was shown to colocalize with PKCα and AMPA receptors at excitatory synapses, possibly conferring substrate specificity on AMPA receptor phosphorylation. On the other hand, PICK1 was demonstrated to induce AMPA receptor clustering in a heterologous expression system (39). Recent studies suggest that NMDA stimulation and the subsequent PKC activation trigger the downregulation of AMPA receptor complexes, through the internalization of AMPA receptors, and increase the amount of GluR2/3 coimmunoprecipitated with PICK1. These observations lead to the suggestion that the NMDA-induced downregulation of the functional AMPA receptors involves the interaction between GluR2/3 subunits and PICK1 (40).

SAP97 was described to associate with GluR1, a long form of AMPA receptor subunits, through the motif TGL on GluR1 C-terminal. SAP97 contains three PDZ domains and, unlike GRIP and PICK1, comprises a Src homology region 3 (SH3) domain and a guanylate kinase (GK) domain (41). SAP97 was reported to be important for recruitment of PKA and PKC through AKAP79/150 (A-kinase anchoring protein). This protein forms a complex with SAP97 that directs PKA to GluR1, facilitating GluR1 S845 phosphorylation (42), and with protein phosphatase PP2B, that acts in opposition to PKA

(43). However, it was described that GluR1-SAP97 interacts predominantly in the biosynthetic and secretory pathway (44).

Syntenin was first found to interact with syndecans (45) and is now known to bind GluR1, GluR2, GluR4, GluR2c, and GluR3c, but the function of these interactions is not known (33). Syntenin contains two PDZ domains that can recognize type I, type II, or non-conserved PDZ-binding motifs and can also dimerize, but the domain responsible for dimerization is currently unknown (46).

Non-PDZ Domain–Containing Proteins. Lyn is a nonreceptor tyrosine kinase highly expressed in the CNS. Immunoprecipitation studies revealed that 1%–2% of Lyn present in the cerebellum is coimmunoprecipitated with GluR2. Lyn was described to interact with the C-terminal sequence of GluR1, GluR2/3, and GluR4c AMPA receptor subunits through its SH3 domain. *In vitro* studies concluded that the GluR2 C-terminal amino acids 813–841 are sufficient for the interaction with Lyn (47). Interaction of AMPA receptors to Lyn enables Lyn tyrosine kinase activation following AMPA receptor stimulation, leading to the activation of a MAPK (mitogen-activated protein kinase) pathway. Lyn activation is probably independent of Ca^{2+} influx, because GluR2 homomeric AMPA receptors are impermeable to calcium, and is probably induced by a receptor conformational change (47).

Narp is a secreted immediate-early gene whose expression is regulated by synaptic activity. Narp is a member of the pentraxin family of proteins characterized by self-multimerization to form pentamers that may dimerize to form decamers. Narp possesses about 200 N-terminal amino acids and a C-terminal pentraxin domain. Immunoprecipitation experiments revealed that Narp associates with GluR1, GluR2, and GluR3 (but not GluR4) AMPA receptor subunits (48). Narp has the ability to cluster AMPA receptors in HEK 293T transfected cells. Narp-Narp association between presynaptic and postsynaptic cells was suggested to contribute to excitatory synapse formation through AMPA receptor clustering as a result of Narp-AMPA receptor interaction. Presynaptic expression of Narp induces the clustering of AMPA receptors in neurons and, postsynaptically, Narp overexpression induces a 2-fold increase in the number of excitatory synapses (48).

Stargazin is a postsynaptic density (PSD) enriched protein thought to contain four transmembrane domains and N- and C-terminal intracellular tails. The stargazin mutant mouse—the stargazer—lacks functional AMPA receptors on cerebellar granulle cells and is an ataxic and epileptic mouse. Stargazin was described as an AMPA receptor–interacting protein, binding GluR1, GluR2, and GluR4 subunits, but the stargazin binding site on AMPA receptor subunits is not known. Stargazin C-terminal contains a type-I PDZ-binding motif (RRTTPV), and it was shown to interact with the PDZ domain–containing proteins PSD-95, SAP-97, PSD-93, and SAP-102 (49). Immunoprecipitation studies showed that stargazin binds both AMPA receptors and PSD-95 and this protein was suggested to play a role in the regulation of AMPA receptor targeting to the membrane surface. Stargazin-mediated synaptic targeting of AMPA receptors is dependent on stargazin binding to PDZ domain-containing proteins (49). The PDZ-binding motif of stargazin was recently shown to be phosphorylated on a threonine at position −2 by PKA, and the mutation of this threonine to a glutamate (that mimics the effect of phosphorylation) abolishes the interaction of stargazin with PSD-95 and interferes with the PSD-95–mediated clustering of stargazin in hippocampal neurons. It was suggested that phosphorylation of the PDZ-binding motif of stargazin is a regulator of synaptic levels of AMPA receptors and synaptic strength (50).

NSF, a protein involved in exocytotic mechanisms, is thought to act after the fusion step, disassembling the complex of proteins involved in membrane fusion. NSF is an ATPase demonstrated to associate with GluR2 in a complex including α and β-SNAPs (soluble NSF attachment proteins) that is stabilized by nonhydrolysable ATPγS (51). The tridimensional structure of NSF seems to be important to maintain this interaction, because all NSF domains are necessary to bind GluR2. On the other hand, it seems that only 10 GluR2 C-terminal amino acids (from L844 to Q853) are responsible for NSF binding (52). The NSF-GluR2 interaction is required for surface expression of GluR2-containing AMPA receptors because disruption of this interaction leads to the removal of most GluR2-containing AMPA receptors from the surface of the cell (53). Deletion of the NSF-binding motif on GluR2-increased NMDA induced internalization of GluR2-containing AMPA receptors, suggesting that binding of NSF to GluR2 stabilizes AMPA receptors in the plasma membrane (35), and this effect involves disruption of the GluR2-PICK1 interaction (54). Recent studies also show that BDNF induces surface translocation of AMPA receptors in cultured neocortical neurons and increases the association of GluR2 and NSF (55).

AP2 is the best-characterized member of the family of heterotetrameric clathrin adaptor complexes that play pivotal roles in many vesicle trafficking pathways within the cell. GluR2 C-terminal segment KRMK is necessary for AP2 binding to the AMPA receptor subunit, and recent results showed that disruption of GluR2-AP2 interaction eliminated long-term depression (LTD) without affecting

basal synaptic transmission. It was also suggested that GluR2 association to AP2, in cultured hippocampal neurons, is necessary for the internalization of GluR2 induced by NMDA receptor activation, but is not required for AMPA-stimulated receptor internalization (56).

A neuronal-specific form of the red blood cell actin cytoskeleton–associated protein 4.1R, the 4.1N protein, associates with the GluR1 C-terminal membrane proximal domain. The association of GluR1 with 4.1N appears to stablize AMPA receptors at the cell surface, possibly by cross-linking them to the cytoskeleton (57).

Work in our laboratory showed that PKC upregulates AMPA receptor activity in chick embryo retinal cultures, where GluR4 is the main AMPA receptor subunit expressed (58,59), and that PKCγ is able to directly bind to GluR4 C-terminal membrane proximal region of the subunit. Our results showed that GST fused to GluR4 C-terminal pulled down PKCγ and that there was phosphorylation of GluR4 S842 within those complexes (24). Recent work showed that in the rat hippocampus, GluR4 S842 phosphorylation by PKA, activated by spontaneous activity early in development, is necessary and sufficient for GluR4-containing AMPA receptors delivery to synapses (22). PKC also phosphorylates GluR4 S842 in transfected HEK 293T (23), and PKCγ expression in GluR4 transfected HEK 293T cells increase GluR4 surface expression upon stimulation with PMA, when compared to PKCγ-deficient cells, arguing for a role for anchored PKCγ in GluR4 receptor subunit phosphorylation and targeting to the plasma membrane (24).

Regulation of AMPA Receptors by Metabotropic Receptors

AMPA receptors are regulated by metabotropic receptors coupled to the activation of phospholipase C (e.g., group I metabotropic glutamate receptors) or to adenylate cyclase (D1-like dopamine receptors) in several different cell types. Receptors from the first group increase the intracellular levels of inositol 1,4,5-triphosphate (IP_3), which releases Ca^{2+} from intracellular stores, and diacylglycerol (DAG), thereby activating PKC (60). Activation of D1-subtype (D_1 and D_5) dopamine receptors increases the intracellular cAMP levels and stimulates PKA (61).

Dopamine D1 receptors were originally shown to enhance kainate-gated ionic conductance (62) and the probability of channel opening (63) in cone-driven horizontal cells from the white perch. Stimulation of D1 receptors in chick spinal motor neurons increased the relative fraction of non-desensitizing kainate-activated channels in a PKA-dependent manner, but it was without effect on the receptor conductance (64). Activation of excitatory dopamine receptors also increased GluR1 phosphorylation on the PKA site Ser845 in cultured neurons from the striatum and the nucleus accumbens and in neostriatal slices (65–67). This effect was associated with a potentiation of the amplitude of AMPA receptor–mediated currents in cultured striatal neurons (65). Phosphorylation of GluR1 was also observed in the neostriatum *in vivo* in response to the psychostimulants cocaine and methamphetamine, suggesting that AMPA receptor phosphorylation secondary to the activation of dopamine receptors plays a role in the effect of psychostimulants (66). Studies in acutely dissociated neostriatal neurons, using as an assay the "rundown" of AMPA currents observed after consecutive stimulation of the receptors, showed that protein phosphatase 1 (PP1) also plays an important role in the regulation of AMPA receptor activity (68). In this preparation, PP1 is thought to keep AMPA receptors dephosphorylated under resting conditions, because it is anchored in the vicinity of the receptors by spinophilin. Stimulation of D1 receptors activates AMPA receptors in neostriatal neurons through a synergistic action, involving direct phosphorylation of the receptor and DARPP-32 (dopamine- and cAMP-regulated phosphoprotein)/PP-1–mediated inhibition of receptor dephosphorylation (68).

Activation of D1 receptors also increases the amount of GluR1 associated with the plasma membrane in cultured neurons from the nucleus accumbens (69). Because adenylate cyclase stimulation with forskolin also increases surface expression of GluR1 in these cells, the phosphorylation of AMPA receptors and their insertion into the membrane following stimulation of D1 receptors may be related events, as shown in cortical and hippocampal cultures (70). In the CA1 region of the hippocampus, dopamine D1-type receptors (D_1/D_5) also enhance AMPA and NMDA receptor–mediated currents, by an unknown mechanism dependent on a postsynaptic $[Ca^{2+}]_i$ rise (71). The effects on AMPA receptors may be due, at least in part, to an increase in the number of GluR1-containing AMPA receptors associated with the plasma membrane, because the translocation of these subunits is increased by PKA phosphorylation and requires CaMKII activity (22).

A potentiation of AMPA receptor activity by group I metabotropic glutamate receptors (mGluR) was also observed in rat spinal cord motoneurons (72,73) and dorsal homn neurons (74,75). (1S,3R)-1-Amino-1, 3-cyclopentanedicarboxylic acid (1S,3R-ACPD), an agonist of group I (mGluR1 and mGluR5) and II (mGluR3 and mGluR4) mGluRs, also potentiated AMPA responses

in a subpopulation of neurons from the rat visual cortex (76,77). In the spinal cord motoneurons the potentiation of AMPA responses by (1S,3R)-ACPD was due to activation of mGluR1/5 and was mediated by PKC (72). However, this kinase was not required for the potentiation of AMPA receptor activity by a specific agonist of mGluR5, suggesting that when mGluR1 and 5 are activated simultaneously the signaling cascade activated by the former type of receptor predominates (73). In contrast with these effects, the group I and II mGluR agonists (1S,3R)-ACPD decreased AMPA responses in cultured chick cerebellar Purkinje neurons, and this effect was antagonized by protein kinase C inhibitors (78). Although the mechanism involved in the depression of AMPA receptor activity was not investigated, it may be related to the effect of group I mGluR in the hippocampus, where these receptors induce the internalization of AMPA receptors by a mechanism dependent on new protein synthesis (79,80).

Interestingly, in cultured retinal neurons there is a cross-talk between D1 receptors and group II mGluRs in the regulation of AMPA receptor activity (13,81). In these cells D1 receptors potentiated the activity of AMPA receptors by activating PKA, and this effect was antagonized by prior activation of group II mGluRs.

AMPA Receptor Trafficking

AMPA receptor subunits are synthesized and assembled in the rough endoplasmic reticulum (ER) and then inserted into the plasma membrane after crossing the Golgi (Fig. 2). Studies using cultured hippocampal neurons showed that cMyc fusion constructs with GluR2 subunit mRNA can be translated in the dendrites, in a regulated manner (82), suggesting that the synthesis of AMPA receptors may also occur away from the cell body. In the hippocampus, where AMPA receptors consist mainly of GluR2/GluR1 and GluR2/GluR3 heteromers (6), a large intracellular pool of GluR2 was found, in association with GluR3 (83). The GluR2 region responsible for the retention of this AMPA receptor subunit is the R residue in the Q/R-editing site in the channel-lining pore, which is lacking in GluR1. The PDZ domain of GluR2 is involved in ER exit, possibly by interacting with PICK1 (83), and this subunit is thought to traffic continuously to ensure the homeostasis of AMPA receptors at active synapses. In contrast to GluR2/3, GluR1 receptors exit the endoplasmic reticulum and progress rapidly through the early secretory pathway, possibly driven by interaction with SAP97 (44). At resting condition, GluR1 appears to have a slower kinetics of surface insertion than GluR2, which, however, is accelerated by NMDA or insulin stimulation (see Section "Modulation of AMPA Receptors in LTP") (84).

Insertion of AMPA receptors into the membrane is likely to involve interaction between soluble *N*-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) complexes: a vSNARE on the vesicles and a t-SNARE on the target membrane. Accordingly, AMPA receptor currents are reduced following application of botulinum toxin (85), which cleaves SNAREs. Furthermore, when the interaction between GluR2 and NSF was blocked using a peptide that mimics the NSF binding site on GluR2, a reduction in the surface expression of GluR2 and in AMPA currents was observed (53,85,86).

AMPA receptors undergo a constant trafficking between the plasma membrane and intracellular compartments. This process plays a key role in the regulation of the synaptic levels of AMPA receptors and has been shown to be regulated by a clathrin-mediated endocytosis (87–89). Immunostaining and coimmunoprecipitation studies have shown that AMPA receptors and clathrin-coated pits are associated when AMPA receptor internalization is promoted. Also, the majority of the internalized AMPA receptors colocalize with a marker of clathrin-mediated endocytosis (EPS15) (88). Inhibition of the endocytotic pathway with hypertonic solutions or by blocking the function of dynamin, that is necessary for clathrin-mediated endocytosis, also blocked AMPA receptor internalization (87,88). These results demonstrate that AMPA receptor endocytosis is mediated by clathrin and suggest that endocytosis is an important mechanism to regulate AMPA receptor activity.

Agonist binding to both AMPA and NMDA receptors can regulate AMPA receptor internalization (70,90–92). However, the fate of the internalized AMPA receptors is determined by the nature of the stimuli. In hippocampal neurons stimulated with NMDA, internalized AMPA receptors are transported rapidly from the membrane to early endosomes and can be recycled, returning to the plasma membrane (70). In contrast, following AMPA receptor activation the receptors are transported to late endosomes, and then probably subjected to lysosomal degradation (70). PKA also exerts a differential modulatory effect on intracellular AMPA receptor trafficking upon AMPA- and NMDA-induced internalization. Indeed, NMDA receptor–induced AMPA receptor trafficking is accompanied by dephosphorylation followed by rephosphorylation of GluR1 AMPA receptor subunits at Ser845 by PKA. In contrast, PKA is without effect on AMPA-induced AMPA receptor cycling (70). The role of AMPA receptor phosphorylation in the

internalization induced by NMDA in cultured hippocampal neurons is further supported by studies showing that the internalization of the GluR1 subunit in response to stimulation with NMDA is inhibited in cultured cells from mice in which both Ser831 and Ser845 in GluR1 were mutated to alanines (93).

Insulin has also been shown to depress the excitatory synaptic transmission by regulating AMPA receptor endocytosis (88,91). Immunostaining of AMPA receptors showed that insulin- and LTD-induced internalization of AMPA receptors is mutually occlusive. Furthermore, in both cases receptor internalization was blocked by inhibiting postsynaptic clathrin-mediated endocytosis, suggesting that AMPA receptor internalization upon insulin treatment and LTD occur by the same mechanism (88). The presence of GluR2 AMPA receptor subunits is required for insulin-induced AMPA receptor internalization (88,91), and the effect of insulin was inhibited by genistein and staurosporin, indicating that a cascade of tyrosine and/or serine/threonine kinases is involved (90).

Role of AMPA Receptor Phosphorylation and Trafficking in Synaptic Plasticity

Long-term potentiation and long-term depression are forms of synaptic plasticity thought to underlie learning and memory processes. LTP refers to a persistent increase in efficacy of synaptic transmission, following a short period of high-frequency synaptic stimulation. In contrast, a reduction in synaptic strength characterizes LTD, following low-frequency synaptic stimulation. Because AMPA receptors mediate most of the fast excitatory neurotransmission, their regulation is thought to be important for these forms of synaptic plasticity. Indeed, there is accumulating evidence suggesting that changes in the phosphorylation of AMPA receptors and in the number of plasma membrane–associated AMPA receptors are associated with LTP and LTD.

Modulation of AMPA Receptors in LTP. GluR1 is phosphorylated by CaMKII during LTP in the hippocampus (94,95), and postsynaptic expression of a constitutively active form of CaMKII in hippocampal slices enhanced synaptic transmission and prevented further LTP induction (96,97), suggesting that CaMKII and LTP enhance synaptic transmission through the same mechanism. Using phosphospecific antibodies against the GluR1 phosphorylation sites, which recognize GluR1 only when Ser845 or Ser831 are specifically phosphorylated, it was shown that both sites are phosphorylated when LTP is induced in the hippocampal CA1 region (95). However, the modulated site depended on the history of the synapse, because high-frequency stimulation of naïve synapses or of previously depressed synapses increased the phosphorylation of Ser831 (the CaMKII phosphorylation site) and Ser845 (the PKA phosphorylation site), respectively (95). LTP was significantly diminished in CA1 pyramidal neurons from organotypical slice cultures expressing a GluR1 mutant with Ser845 replaced by alanine, indicating that this site is required for efficient LTP (22). Recent studies also showed that in adult mice with knockin mutations in the Ser831 and Ser845 phosphorylation sites LTP was greatly reduced in the hippocampal CA1 region, albeit not completely absent, when compared to the wild-type animals (93). Interestingly, mice with mutation in the GluR1 phosphorylation sites also showed an impairment in the retention of rapidly acquired new learning (93). Phosphorylation of GluR1 on Ser831 and Ser845 increases the apparent single-channel conductance (21) and the apparent open-channel probability (20), respectively, and may therefore mediate, at least in part, the potentiation of synaptic transmission during LTP. Furthermore, Ser845 phosphorylation may also promote AMPA receptor insertion in the membrane (22) (see below) and inhibit internalization of the newly inserted receptors (93), thereby stabilizing LTP.

Phosphorylation of AMPA receptor subunits is likely to mediate synaptic plasticity through regulation of synaptic trafficking and surface expression of AMPA receptors, in addition to the effect on channel function. The first evidence that AMPA receptor levels can be rapidly regulated came from electrophysiological studies in the hippocampal CA1 region, showing the existence of excitatory synapses containing functional NMDA receptors but not AMPA receptors (98–100). These synapses were named "silent synapses" because they could not be activated by synaptically released glutamate because NMDA receptors require a membrane depolarization to be activated. However, when cells were depolarized, to enable NMDA receptor activation, AMPA receptor–mediated responses were rapidly detected at the synapse. These results suggested that AMPA receptors could be rapidly inserted in synapses, thereby activating these synapses. This delivery of AMPA receptors to synapses and consequent activation may play an important role in the potentiation of synaptic transmission during LTP.

Most of the AMPA receptors in the adult hippocampus are hetero-oligomers composed of GluR1/GluR2 or GluR2/GluR3. Studies using hippocampal organotypical cultures transiently expressing green fluorescent protein (GFP)-tagged AMPA receptor subunits showed that

induction of LTP causes a rapid translocation of GluR1-GFP to dendritic spines, and this process required activation of NMDA receptors (101). The same experimental approach also revealed that GluR2 subunits are constitutively delivered to synapses, whereas the translocation of GluR1 to the membrane requires high-frequency stimulation of the synapse (10,101). Interestingly, the GluR1 regulatory mechanism is dominant, because heteromeric receptors containing GluR1 and GluR2 subunits behave like the GluR1 subunit (11). The difference between the regulation of GluR1 and GluR2 delivery to the membrane may explain the fact that LTP is absent in mice lacking the GluR1 subunit (102), in contrast with the enhanced LTP observed in mice lacking GluR2 (103).

In vivo studies also showed a reversible increase in the amount of GluR1 and GluR2 subunits present in synaptoneurosomes (a fraction containing the presynaptic and postsynaptic elements of the synapse) isolated from the hippocampal CA1 region upon high-frequency stimulation (104). In this particular region, postsynaptic application of botulinum toxin, which cleaves and inactivates SNAREs, reduced LTP, indicating that membrane fusion events in the postsynaptic membrane are required for LTP (105). These results further suggest that AMPA receptors are added into the postsynaptic membrane during LTP. Induction of LTP in cultured hippocampal neurons by stimulation of postsynaptic NMDA receptors with glycine is also accompanied by a rapid insertion of AMPA receptors at the surface of dendritic membranes and by an increased clustering in synaptic regions. Both processes are blocked by tetanus toxin (106), indicating that AMPA receptors are inserted into synapses via a SNARE-dependent exocytosis during LTP. Also, a chemically induced form of synaptic potentiation, by brief application of NMDA to rat hippocampal slices, was associated with increased levels of GluR1 and GluR2/3 subunits of AMPA receptors in synaptic membrane preparations (107). This effect was inhibited by brefeldin A (107), which prevents protein trafficking between the Golgi apparatus and cell membranes, indicating that the upregulation in the number of plasma membrane–associated AMPA receptors requires a functional secretory pathway. However, it is still not clear whether the increase in the number of membrane-associated AMPA receptors in LTP is due to an increase in the number of intracellular vesicles containing the receptor that fuse with the membrane and/or due to the presence of more receptors in each transport vesicle.

The rapid trafficking of GluR1-GFP receptor subunits to synaptic regions observed in the organotypical hippocampal cultures following high-frequency stimulation resemble that induced by activation of CaMKII and relied on the PDZ interaction site of the receptor subunit (10). Interestingly, phosphorylation of GluR1 on Ser845 by PKA is required for synaptic incorporation induced by CaMKII (22). However, PKA activation alone was not sufficient to induce synaptic incorporation of GluR1 in hippocampal slices, indicating that PKA and CaMKII act in parallel to induce the translocation of the receptor to the membrane (22). Accordingly, inhibition of CaMKII, or inhibition of calpains, suppressed the potentiation of synaptic transmission by NMDA in hippocampal slices, and the associated increase in the number of AMPA receptors present in synaptic membranes (107). Interaction of group II PDZ domain proteins with GluR2 is required for the continuous replacement of the existing GluR2/GluR3 synaptic receptors (11). Studies using sensory neurons showed that the recruitment of AMPA receptors to silent synapses was inhibited by blocking the interaction of GluR2/3 subunits with GRIP (108), further indicating that glutamate receptor–interacting proteins play an important role in their translocation to the membrane.

The small GTPase Ras was recently shown to mediate the NMDA receptor and CaMKII signaling that drives synaptic delivery of AMPA receptors with long cytoplasmic tails during LTP (109). Although the mechanism(s) involved in Ras activation was not investigated, it may be mediated by SynGAP, a Ras GAP (GTPase activating protein) that is tightly bound to PSD-95 as part of a complex of NMDA receptor–associated proteins (110,111). The activity of SynGAP is inhibited upon phosphorylation by CaMKII, and this may constitute the mechanism leading to the activation of p42/p44 MAPK (112). Activity of this kinase is required for LTP in the CA1 region of the hippocampus (113).

In addition to the effects on the trafficking of AMPA receptors to the synapse (see above) changes in the $[Ca^{2+}]_i$ may also control the lateral diffusion of AMPA receptors in hippocampal neurons. Indeed, recent studies showed that raising intracellular Ca^{2+} triggers rapid receptor immobilization and local accumulation on the neuronal surface (114), but how this effect is linked to synaptic plasticity remains to be determined.

Modulation of AMPA Receptors in LTD. Homosynaptic and chemically induced LTD in the CA1 region of the hippocampus causes a persistent decrease in the phosphorylation of GluR1 on Ser845 (a PKA substrate), but not of Ser831 (a PKC and CaMKII substrate), as determined by Western blotting, using phosphospecific antibodies (95,115). Furthermore, reversal of LTP with low-frequency stimulation is associated with a

dephosphorylation of GluR1 on Ser831, but not of Ser845, indicating that the phosphorylation site modulated by low-frequency stimulation depends on the previous experience of the synapse (95,116). In contrast, induction of LTD in hippocampal slices increases GluR2 phosphorylation on Ser880, which is within the GluR2 C-terminal PDZ ligand (117). The role of GluR1 phosphorylation in LTD in the CA1 region of the hippocampus was recently supported by studies showing that LTD was essentially abolished in mutant mice in which both Ser831 and Ser845 in GluR1 were mutated to alanines (93).

Induction of LTD in a hippocampal cell culture model is also correlated with a selective reduction in the number of GluR1 subunits clustered at synapses (118). Generation of LTD *in vivo* was also found to decrease the number of AMPA receptors in synaptoneurosomes, providing further evidence for the role of AMPA receptor endocytosis (104). This redistribution of GluR1 subunits was dependent on the activity of NMDA receptors and suggests that AMPA receptors are removed from the postsynaptic membrane during LTD. The mechanisms involved in receptor internalization following the induction of LTD in hippocampal CA1 neurons was investigated using peptides that block the interaction of the C-terminal region of GluR2/3 with PDZ proteins (117,119). Postsynaptic intracellular perfusion with a peptide that disrupts the interaction of GluR2 with GRIP1, GRIP2/ABP, and PICK1 inhibited LTD, but the role played by PICK1 is still controversial (117,119). Considering that phosphorylation of Ser880 by PKC disrupts the interaction of GluR2 with GRIP, but not with PICK1 (26,27,120), it was proposed that phosphorylation of the receptor subunit during LTD may prevent the interaction with GRIP1 and GRIP2/ABP at the synaptic plasma membrane. This may allow the receptors to be internalized, where they may be stabilized by interaction with PICK1 (117). The internalization of AMPA receptors during homosynaptic hippocampal CA1 LTD is mediated by clathrin (88) and requires the participation of AP2, a clathrin adapter complex that associates with GluR2 (56).

Recent studies showed that Rap, a member of the Ras superfamily of small GTPases, mediates the NMDA receptor–dependent removal of synaptic AMPA receptors (GluR2/GluR3 subunits) receptors during LTD in the hippocampal CA1 region (109). Although it is still not clear how LTD-inducing stimuli increases Rap activity it may arise from the influx of Ca^{2+} ions produced by activation of NMDA receptors (112). The effect of Rap appears to be mediated by p38 MAPK (109), in agreement with reports showing that the kinase acts downstream of Rap (121) and is able to control certain forms of synaptic plasticity (122).

Cerebellar LTD is also associated with changes in the phosphorylation and trafficking of AMPA receptor subunits. Stimuli inducing LTD in cultured cerebellar granule neurons also cause GluR2 phosphorylation at Ser880, thereby reducing the affinity of the receptor subunit to GRIP (120,123), as reported in hippocampal neurons (see above). This may explain the disruption of GluR2 postsynaptic clusters followed by internalization of the protein observed under the same experimental conditions (120). Studies using peptides designed to disrupt the interaction of PICK1-GluR2/3 or using antibodies directed against the PDZ domain of PICK1, as well as expression of mutant PICK1-GST fusion proteins, showed that PICK1 binding to GluR2/3 plays an important role in cerebellar LTD (123). Expression of cerebellar LTD is also thought to require clathrin-mediated internalization of AMPA receptors (89), which depends upon the carboxy-terminal region of GluR2/3 (123). Furthermore, LTD in the cerebellum requires protein kinase C (124), which is crucial for the internalization of AMPA receptors in these cells (123), in contrast with the hippocampus, where the kinase is not required for internalization of GluR2/3 (117).

Long-term depression of excitatory synapses on dopaminergic neurons of the ventral tegmental area (VTA) was also reported recently (125). These neurons play an important role in processing novel and rewarding information and mediate the addictive properties of many drugs of abuse. VTA LTD is also accompanied by a decrease in the number of GluR1 receptor subunits associated with the plasma membrane, but, in contrast with LTD in other systems (e.g., [126]), it requires activation of PKA in the postsynaptic neuron (125).

CONCLUSIONS

The experimental evidences presently available indicate that phosphorylation of AMPA receptor subunits plays an important role in short-and long-term changes in the activity of glutamatergic synapses. The activity of AMPA receptors can be directly modulated by phosphorylation, which also affects the interaction with other intracellular proteins, thereby modulating the recycling and their localization to defined postsynaptic sites. The phosphorylation of AMPA receptors by multiple kinases determines that their activity results from the integration of the various signals received by the cell. Further studies will be required to fully elucidate

the molecular machinery involved in the control of AMPA receptor traffic and how phosphorylation affects the interaction of AMPA receptor subunits with other proteins. This will contribute to the understanding of the mechanisms of homeostasis of the plasma membrane-associated AMPA receptors and of synaptic plasticity.

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