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# REVIEW

# REGULATION OF AMPA RECEPTORS AND SYNAPTIC PLASTICITY

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**Abstract—Neuronal activity controls the strength of excitatory synapses by mechanisms that include changes in the postsynaptic responses mediated by AMPA receptors. These receptors account for most fast responses at excitatory synapses of the CNS, and their activity is regulated by various signaling pathways which control the electrophysiological properties of AMPA receptors and their interaction with numerous intracellular regulatory proteins. AMPA receptor phosphorylation/dephosphorylation and interaction with other proteins control their recycling and localization to defined postsynaptic sites, thereby regulating the strength of the synapse. This review focuses on recent advances in the understanding of the molecular mechanisms of regulation of AMPA receptors, and the implications in synaptic plasticity.**


**Key words: long-term potentiation, long-term depression, glutamate, receptor trafficking, receptor phosphorylation.**

Contents



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E-mail address: cbduarte@ci.uc.pt (C. B. Duarte).
*Abbreviations:* ABP, AMPA receptor-binding protein; AMPAR, AMPA receptor; Arc, activity-regulated cytoskeleton-associated protein; A$\beta$, beta-amyloid; BAR, Bin/amphyphysin/Rvs; BDNF, brain-derived neurotrophic factor; CAM, cell adhesion molecule; CaMKII, $Ca^{2+}$- and calmodulin-dependent protein kinase II; cGKII, cGMP-dependent protein kinase II; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; FRAP, fluorescence recovery after photobleaching; GFP, green-fluorescent protein; GluR$\delta$2, $\delta$2 glutamate receptor; GRIP, glutamate receptor interacting protein; LBD, ligand-binding domain; LTD, long-term depression; LTP, long-term potentiation; MAGUK, membrane-associated guanylate kinase; MAPK, mitogen-activated protein kinase; mEPSC, miniature excitatory postsynaptic current; mGluRs, metabotropic glutamate receptors; Narp, neuronal-activity-regulated pentraxin; NCAM, neural cell adhesion molecule; NMDA, *N*-methyl-D-aspartate; NMDAR, *N*-methyl-D-aspartate receptor; NPR, neuronal pentraxin receptor; NPRAP, neural plakophilin-related arm protein; NP1, neuronal pentraxin 1; PDZ, postsynaptic density 95/disc large/zonula occludens-1; PICK1, protein interacting with C-kinase-1; PI3-K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PSA, polysialic acid; PSD, postsynaptic density; SEP, superecliptic pHluorin; Ser, serine; SNARE, soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors; TARP, transmembrane AMPA receptor regulatory proteins; TM, transmembrane; TNF$\alpha$, tumor necrosis factor-$\alpha$.

Glutamate is the major excitatory neurotransmitter in the brain, and its effects are mediated by activation of ionotropic and metabotropic receptors, differing in their molecular, biochemical pharmacological and physiological properties (Hollmann and Heinemann, 1994; Kew and Kemp, 2005). The ionotropic glutamate receptors have been classified into three major subtypes, AMPA, kainate, and *N*-methyl-D-aspartate (NMDA) receptors, named after their most selective agonist (Watkins et al., 1981). AMPA receptors (AMPARs) are responsible for the primary depolarization in glutamate-mediated neurotransmission and play key roles in synaptic plasticity. Long-lasting and activity-dependent changes in synaptic strength (long-term potentiation, LTP, or long-term depression, LTD) are associated with changes in the phosphorylation and cellular distribution of AMPAR, and are thought to underlie learning and memory formation (Rumpel et al., 2005; Morris, 2006; Pastalkova et al., 2006; Whitlock et al., 2006). Deregulation of AMPAR activity is also involved in pathology [e.g. (Kwak and Weiss, 2006; Liu et al., 2006)]. This review will concentrate on the molecular mechanisms of regulation of AMPARs, and their implications in synaptic plasticity.

## EXPRESSION OF AMPARs

AMPARs consist of four closely related genes, with about 70% sequence homology (Collingridge et al., 2004), that encode the four subunits GluR1-4 or A–D (Laube et al., 1998; Mano and Teichberg, 1998; Rosenmund et al., 1998). *In situ* hybridization studies, receptor autoradiography using [$^3$H]AMPA and [$^3$H]glutamate as ligands, and immunocytochemistry with antibodies raised against GluR1–GluR4 subunits [reviewed in (Hollmann and Heinemann, 1994; Petralia et al., 1999)] showed a widespread distribution of AMPARs in the brain, as expected from their key role in excitatory neurotransmission. GluR1–GluR3 subunits are enriched in the outer layers of the cerebral cortex, hippocampus, olfactory regions, basal ganglia, lateral septum and amygdala (Kein-

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anen et al., 1990; Beneyto and Meador-Woodruff, 2004). The GluR4 subunit is present in lower amounts throughout the CNS, except in the reticular thalamic nuclei and the cerebellum, where this subunit is also abundant (Petralia and Wenthold, 1992; Martin et al., 1993; Spreafico et al., 1994). The expression of AMPAR subunits is also differentially regulated during development (Petralia et al., 1999; Palmer et al., 2005b; Talos et al., 2006), and although they are regarded as neuronal receptors, they have also been detected in glial cells (Gallo and Russell, 1995; Janssens and Lesage, 2001; Lin and Bergles, 2004).

A recent study using quantitative fluorescence *in situ* hybridization demonstrated that endogenous mRNAs encoding AMPAR subunits GluR1 and GluR2 are localized to proximal and distal dendrites of hippocampal neurons and that a substantial fraction of synaptic sites contain GluR2 mRNA clusters (Grooms et al., 2006). The presence in dendrites of the machinery necessary for protein synthesis, together with the mRNA for AMPAR subunits, suggests that local synthesis of AMPAR subunits regulates local receptor abundance and composition (Steward and Levy, 1982; Kacharmina et al., 2000; Tang and Schuman, 2002; Asaki et al., 2003; Ju et al., 2004; Grooms et al., 2006). Accordingly, chronic activity blockade increases the synthesis of GluR1 in dendrites, and acute activation of group I metabotropic glutamate receptors (mGluRs) or acute depolarization with KCl increases the synthesis of both GluR1 and GluR2 (Ju et al., 2004). Also, dopamine receptor activation promotes transport of endogenous mRNAs, including those from GluR1 and GluR2 in hippocampal neurons (Smith et al., 2005). Interestingly, *in situ* hybridization studies also demonstrate the presence of mRNA encoding proteins relevant in the regulation of the excitatory synapses, such as microtubule-associated protein 2 (MAP2), the $\alpha$-subunit of $Ca^{2+}$- and calmodulin-dependent protein kinase II (CaMKII-$\alpha$), brain-derived neurotrophic factor (BDNF), activity-regulated cytoskeleton-associated protein (Arc), TrkB receptor, inositol-1,4,5-trisphosphate ($Ins(1,4,5)P_3$) receptor, the atypical protein kinase M$\zeta$, the NMDA receptor (NMDAR) NR1 subunit, and glycine receptor $\alpha$ subunit in dendritic layers of hippocampus and in dendrites of hippocampal neurons *in vivo* and *in vitro* [for reviews, see (Martin and Zukin, 2006; Schuman et al., 2006)]. Localization of mRNAs and regulated translation in dendrites have recently gained widespread acceptance as mechanisms fundamental to synaptic plasticity (Eberwine et al., 2001; Steward and Schuman, 2003; Martin and Zukin, 2006; Schuman et al., 2006).

## AMPAR STRUCTURE AND DIVERSITY

AMPARs are largely $Ca^{2+}$-impermeable, display exceptionally fast kinetics and mediate moment-to-moment synaptic signaling (Jonas, 2000). These characteristic functional properties depend on the subunit composition and on subunit modifications introduced by alternative splicing.

The AMPAR GluR1–GluR4 subunits combine in tetramers in different stoichiometries (Hollmann and Heinemann, 1994), which determine channel function (i.e. desensitization/resensitization kinetics and conductance properties) (Ozawa et al., 1998) and trafficking to synapses (Malinow et al., 2000). Stargazin and other transmembrane (TM) AMPA receptor regulatory proteins (TARPs) also coassemble stoichiometrically with native AMPARs. The TARPs act as auxiliary subunits that are required for AMPAR maturation and trafficking, and modulate channel function (see below) (Korber et al., 2007; Ziff, 2007).

Each AMPAR subunit comprises about 900 amino acids and has a molecular weight of about 105 kDa. The GluR1–GluR4 subunits share 68–74% amino acid sequence identity (Collingridge et al., 2004) and contain four hydrophobic domains: TM1, TM3, and TM4 transverse the membrane, while M2 faces the cytoplasm as a reentered loop that forms part of the channel pore (Fig. 1A). The N-terminal segment is homologous to the bacterial leucine-isoleucine-valine binding protein (LIVBP), while the adjacent ligand-binding domain (LBD) is homologous to glutamine binding protein (Madden, 2002). The LBD is split into the S1 and S2 segments by TM segments. Ligand binding to the LBD initiates conformational changes that are transduced to the TM segments and trigger opening of the channel's gate (Gouaux, 2004; Mayer, 2005). All three modules—the N-terminus, the LBD, and the ion-channel domain—are engaged in distinct, interdependent subunit-subunit interactions (Greger et al., 2006). The C-terminal part of S2 is not directly involved in agonist binding and, due to alternative RNA splicing, is expressed in two forms, flip and flop, that differ in a few amino acids only, but which result in receptors with different desensitization and endoplasmic reticulum (ER) export kinetics (Sommer et al., 1990; Mosbacher et al., 1994; Coleman et al., 2006). A recent study from our laboratory identified versions of the AMPAR subunits that lack both the flip and flop exons, and play a dominant negative role (Gomes et al., 2007b).

Finally, the C-terminus of AMPAR subunits is intracellular and shows differences between the subunits. GluR1, GluR4, and an alternative splice form of GluR2 (GluR2L) have longer cytoplasmic tails with high homology (Fig. 1B). In contrast, the predominant splice form of GluR2, GluR3, and an alternative splice form of GluR4 (GluR4c) have shorter, homologous cytoplasmic tails (Fig. 1B). Receptors composed of subunits with short cytoplasmic C-termini (GluR2/3) cycle continuously in and out of the synapse, with a time constant of about 15 min (Passafaro et al., 2001; Shi et al., 2001), whereas receptors containing long C-termini (GluR1/2 and GluR2/4) are added into synapses in an activity-dependent manner (Hayashi et al., 2000; Shi et al., 2001). Each subunit binds specific intracellular proteins through the C-terminal tail, and these interactions play important roles in controlling the trafficking of AMPARs and/or their stabilization at the synapses.

## AMPAR POST-TRANSLATIONAL MODIFICATIONS

Phosphorylation is a key post-translational modification in regulating AMPAR function (Carvalho et al., 2000). It can

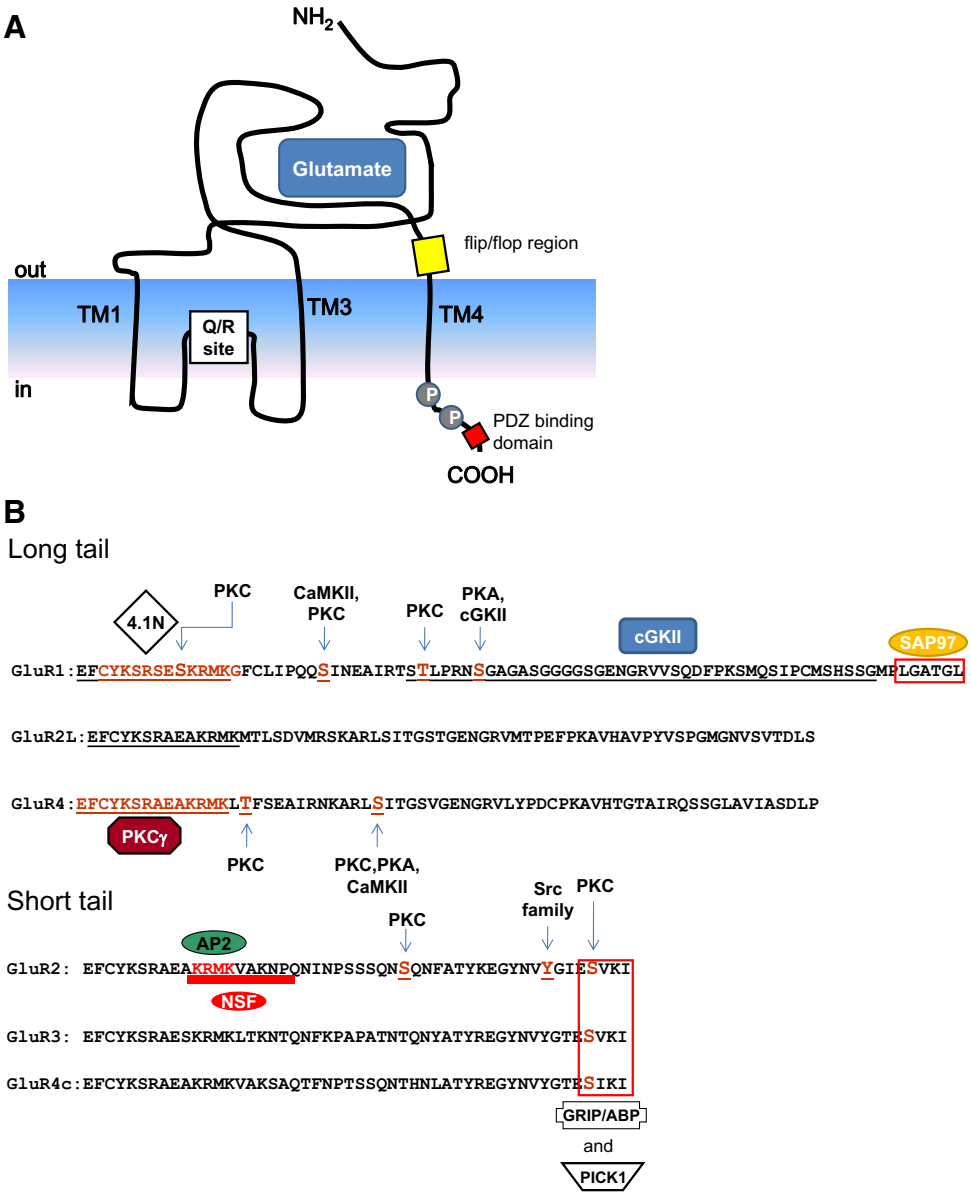


**Fig. 1.** Schematic representation of the topology of AMPA receptor subunits (A). Sequence alignment of the intracellular C-terminal regions of the long-tailed (GluR1, GluR2L and GluR4) and short-tailed (GluR2, GluR3 and GluR4c) AMPA receptor subunits. The protein binding sites on AMPA receptor subunits (boxes) and the phosphorylation sites are underlined and indicated with a larger font size.

regulate the physiological properties of the channel as well as protein trafficking (Fig. 2). GluR1 subunit has been described to be phosphorylated at three serine residues located in the intracellular C-terminus: serine 831 (Ser831) can be phosphorylated by both protein kinase C (PKC) (Roche et al., 1996) and CaMKII (Mammen et al., 1997); serine 845 (Ser845) is a protein kinase A (PKA) and cGMP-dependent protein kinase II (cGKII) phosphorylation site (Roche et al., 1996; Serulle et al., 2007) and serine 818 (Ser818) is a substrate for PKC (Fig. 1B) (Boehm et al., 2006). LTP induction increases the CaMKII-dependent phosphorylation of GluR1 at Ser831 (Mammen et al., 1997). Although such phosphorylation may enhance the function of synaptic receptors (Benke et al., 1998), it does not seem to be required for receptor synaptic delivery, since mutations on GluR1-Ser831 that prevent its phosphorylation by CaMKII do not prevent delivery of the receptor to synapses by active CaMKII (Hayashi et al., 2000). Interestingly, mutations at Ser845, the PKA phosphorylation site of GluR1 (Roche et al., 1996), do prevent delivery of GluR1 to synapses by active CaMKII (Esteban et al., 2003a). On the other hand, PKA activity is necessary but not sufficient for the CaMKII-driven incorporation of GluR1 into synapses (Esteban et al., 2003a). It is important to note that both Ser831 and Ser845 are necessary, but not sufficient, to deliver AMPARs into synapses, which requires the activation of the CaMKII–Ras–MAPK (mitogen-activated protein kinase) pathway (Esteban, 2003b).

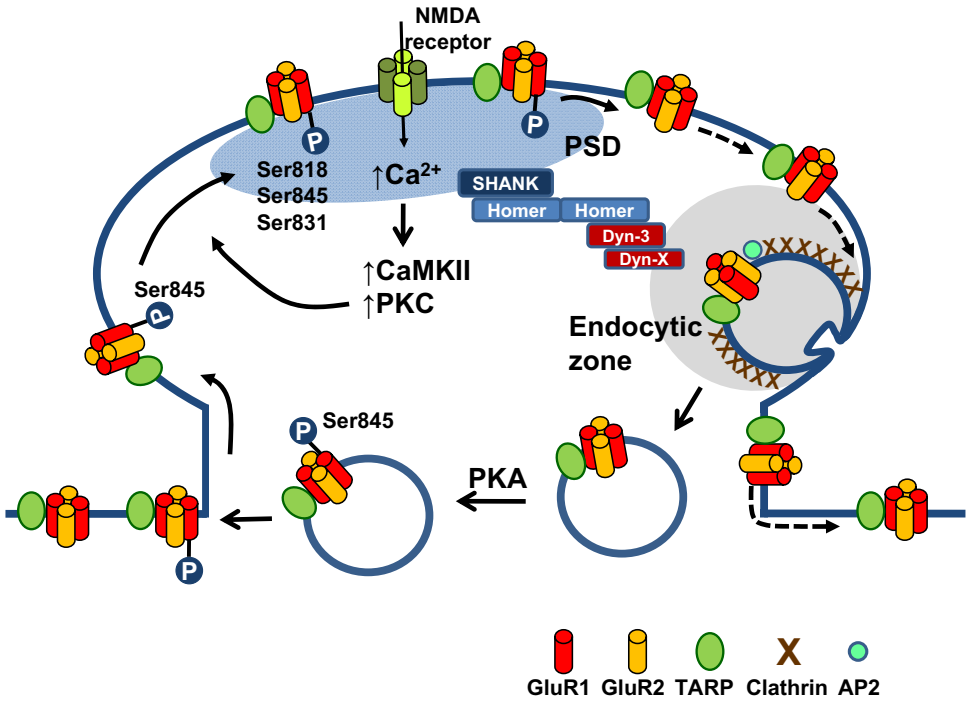


**Fig. 2.** Regulation of the intracellular traffic of GluR1-containing AMPA receptors. The intracellular pool of receptors is delivered to the synapse in an activity-dependent manner. The population of AMPA receptors present in the PSD has a limited mobility, in contrast with the non-synaptic receptors which diffuse in the membrane. The receptors internalized at the endocytic zone by a clathrin-mediated process may be then recycled. See text for further details.

Phosphorylation of GluR1 Ser818 by PKC is critical in LTP-driven incorporation of AMPARs into the postsynaptic membrane (see below) and is suggested to exert its function by facilitating the interaction between GluR1 and a delivery or tethering protein (Boehm et al., 2006).

In addition to the serine residues, recent work from Lee et al. (2007) reported threonine 840 (Thr840) as one of the major phosphorylation sites in GluR1. This site is phosphorylated by PKC *in vitro* and shows a high turnover rate under basal conditions in the hippocampus.

PKC also phosphorylates the GluR2 subunit. In this case, the phosphorylation occurs at the C-terminal sequence (IESVKI) within the PDZ (postsynaptic density 95/disc large/zonula occludens-1) domain binding region through which GluR2 binds to different proteins (glutamate receptor interacting protein (GRIP)/ABP and protein interacting with C-kinase-1 (PICK1), see below), therefore modulating those interactions (Chung et al., 2000; Matsuda et al., 2000; Seidenman et al., 2003). Phosphorylation of GluR2 (Ser880) by PKC (Fig. 1B) decreases receptor binding to GRIP1, recruits PICK1 to excitatory synapses and facilitates rapid internalization of surface receptors (Chung et al., 2000). Chung et al. (2003) demonstrated that GluR2 phosphorylation at Ser880 is a critical event in the induction of cerebellar LTD (see below).

GluR2 is also phosphorylated at tyrosine 876 (Tyr876) in its C-terminus by the Src family protein tyrosine kinases, *in vitro* and *in vivo* (Fig. 1B) (Hayashi and Huganir, 2004). Interestingly, phosphorylation of this tyrosine residue has similar effects to the phosphorylation of Ser880. Phosphorylation of GluR2 on Tyr876 decreases the binding to GRIP1/ABP, but is without effect on the binding to PICK1, thus facilitating the AMPA- or NMDA-induced receptor internalization (Hayashi and Huganir, 2004).

GluR4 is expressed in the hippocampus during the early postnatal period, and spontaneous activity at this stage is sufficient to trigger GluR4 synaptic incorporation (Zhu et al., 2000). Phosphorylation of GluR4 at serine 842 (Ser842) by PKA (Fig. 1B) (Carvalho et al., 1999) is both necessary and sufficient for the delivery of GluR4-homomeric receptors to the synapse (Esteban et al., 2003a), and is regulated by metabotropic glutamate and dopamine receptors in retina cells (Gomes et al., 2004). In addition, PKC$\gamma$ interacts directly with GluR4 and phosphorylates Ser842 *in vitro* (Correia et al., 2003) and in cultured retina cells (Gomes et al., 2004). Disruption of this interaction prevents efficient receptor phosphorylation by PKC and the PKC-driven increase in cell surface expression of GluR4-containing AMPARs (Gomes et al., 2007a).

Protein palmitoylation is a reversible fatty acid acetylation that regulates protein trafficking and cellular localization. All AMPAR subunits can be palmitoylated on two cysteine residues in their membrane domain M2 and in their C-terminal region, *in vitro* and *in vivo* (Hayashi et al., 2005). Palmitoylation on M2 is upregulated by the palmitoyl-acyl transferase GODZ and leads to an accumulation of the receptor in the Golgi and a reduction of receptor surface expression. On the other hand, when palmitoylation occurs at the C-terminal domain it contributes to receptor internalization, by inhibiting receptor interaction

with the 4.1N protein (Hayashi et al., 2005), which has previously been shown to stabilize AMPAR expression on the cell surface (Shen et al., 2000). Moreover, activation of GluRs by glutamate stimulation decreases receptor palmitoylation and recruits more AMPARs to the cell surface (Hayashi et al., 2005). Together these evidences suggest that palmitoylation may play important roles in the postsynaptic trafficking of AMPAR and in the regulation of excitatory synaptic transmission.

## AMPAR TRAFFIC

### AMPAR biosynthesis and AMPAR interaction partners

AMPAR subunits are synthesized and assembled in the rough endoplasmic reticulum (ER) and then inserted into the plasma membrane after crossing the Golgi apparatus. The assembly of AMPARs in the ER and subsequent ER exit is influenced by subunit-specific interactions and RNA editing of GluR2 at the Q/R site (Greger and Esteban, 2007). GluR2 is a critical subunit in determining mammalian AMPAR function. Most mature GluR2 protein contains an arginine residue (R) within the re-entrant M2 membrane loop region at position 586 in place of the genomically-encoded glutamine (Q) (Sommer et al., 1991). This Q/R editing (Fig. 1A) is specific to the GluR2 subunit and more than 95% of GluR2 mRNA transcripts are edited in the postnatal brain. The Q/R site provides a key ER quality control checkpoint, since editing to Arg attenuates the formation of GluR2 homo-tetramers and establishes a stable GluR2 pool in the ER (Greger et al., 2002). This subunit appears to require assembly into heteromeric channels for ER export (Greger et al., 2003), and prolonged GluR2 ER residence may be a prerequisite for the formation of GluR2-containing heteromeric AMPARs later in development.

TARPs coassemble with AMPARs early in the synthetic pathway and control their maturation, trafficking, and biophysical properties (Nicoll et al., 2006; Ziff, 2007). Stargazin was originally identified as the mutant gene in the Stargazer mouse, which exhibits profound cerebellar ataxia and epilepsy (Osten and Stern-Bach, 2006), resulting from the lack of functional AMPAR channels in cerebellar granule cells (Chen et al., 2000; Schnell et al., 2002). This family of proteins comprises five isoforms: $\gamma$-2 (or Stargazin), $\gamma$-3, $\gamma$-4, $\gamma$-7, and $\gamma$-8, all of which share a weak homology to the $\gamma$ subunits of muscle voltage-dependent $Ca^{2+}$ channels (VDCCs) (Burgess et al., 1999; Klugbauer et al., 2000). These proteins contain four TM domains and their carboxy terminus interact with the PDZ domains of postsynaptic density (PSD) 95 and with other membrane-associated guanylate kinase (MAGUK) family members (Chen et al., 2000).

Biochemical and cell biology studies have shown that TARPs are involved in folding and assembly of AMPAR, stabilizing and facilitating their export from the ER (Tomita et al., 2003; Vandenberghe et al., 2005). Furthermore, TARPs promote AMPARs surface expression (Chetkovich et al., 2002; Schnell et al., 2002; Tomita et al., 2003) and are critical for clustering AMPARs at excitatory synapses through their interaction with PSD-95 (Chen et al., 2000; Schnell et al., 2002), a major component of the postsynaptic scaffold (Kim and Sheng, 2004), and probably with other MAGUKs (Elias et al., 2006). Schnell et al. (2002) observed that PSD-95 overexpression in hippocampal slices enhances specifically synaptic AMPAR-mediated response without changing the number of surface AMPARs. Conversely, they describe that Stargazin overexpression increases selectively the number of extrasynaptic AMPARs without changing AMPAR-mediated synaptic currents. These observations indicate that the Stargazin/PSD-95 interaction is involved in the stabilization of AMPARs at synapses.

In addition to the effect on AMPAR trafficking, Stargazin controls AMPAR channel gating by slowing glutamate-induced AMPAR deactivation and desensitization, and enhancing the channel conductance (Priel et al., 2005; Tomita et al., 2005; Nicoll et al., 2006). Moreover, in the presence of TARPs, the AMPARs competitive antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) acts as a partial agonist (Menuz et al., 2007). These results, together with the resolution of the crystal structure of CNQX bound to the TARP-less AMPAR LBD (Menuz et al., 2007), led the authors to propose a model where TARPs either strengthen the coupling between agonist-induced domain closure and channel opening, perhaps by promoting linker separation, or directly enhance the degree of domain closure induced by CNQX.

The final step of insertion of the receptors in the synaptic membrane involves tightly regulated events that depend on the subunit composition of the receptor and on specific signals contained within the C-termini. Several PDZ domain-containing proteins have been shown to participate in the process. The final four amino acids at the C-terminus of GluR1 form a group I PDZ ligand, while the tails of GluR2, GluR3 and GluR4c form group II PDZ ligands. GluR4 and GluR2L have distinct C-terminal tails and it is unclear whether they interact with classical PDZ domains. GluR1 was described to interact with SAP97 (Fig. 1B) (Leonard et al., 1998). The interaction between SAP97 and GluR1 first occurs in the receptor secretory pathway and is essential for the transport of the receptor from the ER to the *cis* face of the Golgi apparatus, with SAP97 dissociating from the complex at the plasma membrane (Sans et al., 2001). Also RIL [reversion-induced LIM gene (Schulz et al., 2004)] is an interactor for GluR1 and may be involved in actin-dependent trafficking of GluR1. Another actin adaptor, protein 4.1N, also associates with AMPARs and appears to stabilize the surface expression of GluR1 (Shen et al., 2000).

GRIP (Dong et al., 1997), AMPA receptor-binding protein (ABP), also known as GRIP2 (Srivastava et al., 1998), and PICK1 (Dev et al., 1999; Xia et al., 1999) can interact with the PDZ ligand at the extreme C-terminus of GluR2 and GluR3 (Fig. 1B) (Sheng and Sala, 2001). Mutations of the GluR2 PDZ binding site that selectively block GluR2 binding to ABP and GRIP accelerate GluR2 endocytosis at synapses (Osten et al., 2000). These findings identify ABP and GRIP as anchors that contribute to AMPAR synaptic

abundance. Phosphorylation of GluR2 by PKC at Ser880 within the PDZ binding region prevents the association of GluR2 with ABP and GRIP, but not with PICK1 (Matsuda et al., 1999, 2000; Chung et al., 2000). PICK1 besides interacting with GluR2/3 C-terminus also interacts with PKC$\alpha$, and it has been proposed that dimeric PICK1 can act to chaperone activated PKC and AMPARs (Chung et al., 2000; Perez et al., 2001). Several studies indicate that PICK1 regulates the surface expression of GluR2 (Perez et al., 2001; Terashima et al., 2004), and it has recently been shown, in a study using pHluorin-tagged GluR2 and fluorescence recovery after photobleaching (FRAP), that the phosphorylation state of GluR2 Ser880 residue, as well as binding of PICK1 to GluR2, regulates the rate of GluR2 recycling to the plasma membrane after NMDA receptor activation (Lin and Huganir, 2007).

GluR2 also binds NSF, an ATPase required for membrane fusion events (Rothman, 1994), which interacts with a membrane proximal segment of the C-terminus of GluR2 (Fig. 1B) (Nishimune et al., 1998; Osten et al., 1998; Song et al., 1998). This protein helps to maintain the synaptic expression of GluR2-containing AMPARs (Noel et al., 1999; Hanley et al., 2002). NSF displaces PICK1 from the PICK1-GluR2 complex and thereby facilitates the delivery or stabilization of GluR2 at the plasma membrane (Hanley et al., 2002).

Recent work demonstrates a role for AMPAR N-terminal protein–protein interactions either in receptor traffic or in synaptogenesis, which requires neurotransmitter receptors' recruitment to the development of postsynaptic specializations. Via its extracellular N-terminal domain, GluR2 promotes the formation and growth of dendritic spines in cultured hippocampal neurons (Passafaro et al., 2003), and overexpression of that domain increases the frequency of miniature excitatory postsynaptic currents (mEPSCs) (Saglietti et al., 2007). This mechanism has been described to involve a direct interaction of GluR2 N-terminal domain with N-cadherin, suggesting that GluR2 promotes spines and synapse formation by a structural interaction between its N-terminal domain and the presynaptic terminal (Saglietti et al., 2007).

Members of the pentraxin family have been shown to cluster AMPARs (O'Brien et al., 1999; Sia et al., 2007). This family consists of neuronal-activity-regulated pentraxin (Narp) and neuronal pentraxin 1 (NP1), both secreted proteins homologous to the serum pentraxins (Schlimgen et al., 1995; Tsui et al., 1996), and neuronal pentraxin receptor (NPR), an integral membrane protein (Dodds et al., 1997). Narp and NP1 coimmunoprecipitate with AMPARs in heterologous cells (Xu et al., 2003), and Narp-expressing HEK cells seeded on neurons recruit GluR1 to sites where they contact neuronal dendrites (O'Brien et al., 1999). Recently, Sia et al. (2007) described that the presynaptically secreted NP1 and NPR bind to the GluR4 N-terminal domain and are critical trans-synaptic factors for GluR4 recruitment to synapses.

**AMPAR regulation by cell adhesion molecules (CAMs)**

Synaptic CAMs are known to play key roles in various aspects of dendritic spine structure and function, including early differentiation, maintenance, and plasticity. On the other hand, distribution of functional AMPARs is tightly correlated with spine geometry (Matsuzaki et al., 2001, 2004), and recent evidences suggest that CAMs can regulate AMPARs.

Integrins are TM heterodimers of $\alpha$- and $\beta$-subunits (Giancotti and Ruoslahti, 1999; Coppolino and Dedhar, 2000; Schwartz and Shattil, 2000; van der Flier and Sonnenberg, 2001) and have been recently directly implicated in hippocampal LTP (Chan et al., 2006; Huang et al., 2006; Kramar et al., 2006). Infusion of an integrin ligand (the peptide GRGDSP) into rat hippocampal slices reversibly increased the slope and amplitude of excitatory postsynaptic potentials mediated by AMPARs (Kramar et al., 2003). In addition, it was shown that basal excitatory synaptic transmission through AMPARs (Chan et al., 2006) and LTP in the hippocampus are impaired in beta1-integrin knockout mice (Chan et al., 2006; Huang et al., 2006). These results suggest that synaptic integrins regulate glutamatergic transmission and this may occur through AMPARs.

Cadherins also play a role in AMPAR regulation. This family of proteins consist of homophilic adhesion molecules with five extracellular subdomains separated from the cytoplasmic domain by a single TM segment (Takeichi, 1990). Recently, several reports have shown that N-cadherin and its cognate cytoplasmic interacting protein beta-catenin regulate synaptic structure and functions in an activity-dependent manner (Murase et al., 2002; Togashi et al., 2002; Yu and Malenka, 2003). This is of a particular interest because N-cadherin has been shown to be modified by neuronal activity and to play important roles in synaptic plasticity (Tang et al., 1998; Bozdagi et al., 2000; Tanaka et al., 2000). N-cadherin associates and co-localizes with AMPARs in neurons, in a *cis* manner, and this association is regulated by the extracellular $Ca^{2+}$ concentration (Nuriya and Huganir, 2006). AMPAR-N-cadherin interaction regulates AMPAR trafficking by increasing receptor surface expression both in heterologous cells and in neurons (Nuriya and Huganir, 2006). Another study demonstrated that cadherin can anchor AMPARs in complex with ABP/GRIP through a neural plakophilin-related arm protein (NPRAP; also called $\delta$-catenin) (Silverman et al., 2007), which binds to the juxtamembrane region of the cadherin intracellular domain. NPRAP also binds PSD-95, which is a scaffold for NMDA receptors, for AMPARs in complexes with the TARP auxiliary subunits, and for adhesion molecules. Together these data suggest that the association of N-cadherin with AMPARs regulates AMPAR trafficking, and may provide a biochemical link between morphological plasticity and functional plasticity at dendritic spines.

Reelin is a large molecule of the extracellular matrix (ECM) which regulates neuronal positioning during the early stages of cortical development in vertebrate species.

Reelin is also expressed in the adult brain, notably in the cerebral cortex, where it plays an important role in neuronal maturation, synaptic plasticity, and memory formation (Nimpf and Schneider, 2000; Weeber et al., 2002; Beffert et al., 2005; D'Arcangelo, 2005). Its action is mediated through the binding to two types of receptors: apoER2 (apolipoprotein E receptor 2) and VLDLR (very-low-density lipoprotein receptor). Qiu et al. (2006) found that reelin application to adult mice hippocampal slices leads to enhanced glutamatergic transmission mediated by NMDARs and AMPARs, through distinct mechanisms. They proposed that reelin signaling leads to activation of phosphatidylinositol 3-kinase (PI3-K) (Beffert et al., 2002), which drives the intracellular pool of AMPARs for synaptic delivery (Man et al., 2003), favoring synaptic transmission at resting membrane potentials.

A variety of proteins from the immunoglobulin-like family, such as Thy-1, NCAM, L1, contactin, telencephalin and neuroplastin-65 are associated with alterations in hippocampal synaptic plasticity, including LTP and LTD (Muller et al., 1996; Nosten-Bertrand et al., 1996; Bliss et al., 2000; Nakamura et al., 2001; Murai et al., 2002). Empson et al. (2006) showed that homophilic binding by neuroplastin-65 causes a sustained increase in phosphorylation of p38 MAPK, coincident with the p38 MAPK-sensitive loss of LTP and reduced surface expression of the GluR1 AMPAR subunit.

Polysialic acid (PSA) is a negatively charged carbohydrate that is predominantly carried by the neural cell adhesion molecule (NCAM) in mammals. NCAM and, in particular, PSA play important roles in cellular and synaptic plasticity. Making use of artificial lipid bilayers and of PSA from bacterial origin, Vaithianathan et al. (2004) recorded from single channels and demonstrate that colominic acid (polymer of N-acetylneuraminic acid) can dramatically prolong AMPAR channel open time. In addition, colominic acid increased AMPARs currents in immature but not in mature CA1 pyramidal cells (Vaithianathan et al., 2004). These data reveal an age-dependent interaction between PSA and AMPARs that may modulate neuronal transmission and plasticity in the developing CNS.

### Vesicular traffic, synaptic targeting and lateral membrane diffusion of AMPARs

Fast changes in the number of synaptic AMPARs occur during synaptic plasticity, and are probably accounted for by a combination of direct insertion/removal of AMPARs at synaptic and/or extrasynaptic sites and by their lateral diffusion to and from synapses, where they are stabilized by scaffold proteins in the PSD or by binding to extracellular ligands (Fig. 2). AMPARs are inserted at the cell surface through SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors) -dependent exocytosis (Lledo et al., 1998; Luscher et al., 1999), and are removed by rapid ligand-induced endocytosis (Carroll et al., 1999; Man et al., 2000). Moreover, synaptic AMPARs are relatively immobile when compared with extrasynaptic AMPARs, as determined by optical monitoring of the surface trafficking of single receptors using quantum dots coupled to antibodies that recognize the extracellular region of AMPARs (Groc and Choquet, 2006). Local synaptic activity immobilizes GluR1-containing AMPARs at individual synapses (Ehlers et al., 2007).

The mechanisms regulating AMPAR exocytosis are subunit specific, since the exocytosis of the GluR2 subunit is rapid and constitutive, whereas GluR1 exocytosis is slow but inducible (Passafaro et al., 2001). In a recent study, real-time measurements of receptor exocytosis onto the surface of neurons have been performed in organotypic hippocampal slice cultures using time-lapse two-photon laser microscopy and AMPAR subunits tagged with superecliptic pHluorins (SEP), green-fluorescent protein (GFP) variants with strong pH-dependent fluorescence (Kopec et al., 2006). Bath application of a solution that favors NMDAR activation, thereby strengthening glutamatergic synapses (see below), selectively increases GluR1-containing receptors on spine surfaces with no significant net change on the nearby dendrite (Kopec et al., 2006). Accordingly, Gerges et al. (2006) found that overexpression of a dominant negative form of an exocyst subunit (Exo70) impairs constitutive and regulated receptor insertion at the spine surface, and produces an accumulation of AMPARs intracellularly in spines, suggesting that exocytic vesicles containing AMPARs bud from intra-spine compartments into the synaptic surface. However, several studies suggest that exocytosis of AMPARs occurs predominantly at extrasynaptic sites. The real-time trafficking of native AMPARs was followed electrophysiologically, after silencing surface AMPARs using a photoreactive, irreversible antagonist of AMPARs (Adesnik et al., 2005). In this study, it was found that fast cycling of surface AMPARs with receptors from intracellular stores occurs exclusively at extrasynaptic somatic sites, and that the cycling of synaptic AMPARs occurs on a much longer timescale, suggesting that the newly inserted extrasynaptic AMPARs travel laterally along dendrites to synapses (Adesnik et al., 2005). Recently, visualization of discrete exocytic events mediating surface delivery of SEP-AMPARs in hippocampal slice cultures and in dissociated pyramidal neurons was reported (Yudowski et al., 2007). Yudowski and colleagues presented evidences suggesting that a major pathway for surface insertion of AMPARs is via exocytosis of AMPAR-carrying vesicles at extrasynaptic sites. These authors observed persistent exocytic events that dispersed slowly without producing a large increase in the surface receptor fluorescence at adjacent sites, and transient exocytic extrasynaptic events, which were capable of producing increased surface receptor fluorescence on nearby spines. This suggests that the transient exocytic events can drive surface delivery of AMPARs preferentially to nearby spines, eventually by long-range lateral diffusion.

The role of lateral diffusion in AMPAR trafficking has recently been investigated using novel methods that allow single receptor monitoring (Borgdorff and Choquet, 2002; Tardin et al., 2003; Groc et al., 2004; Bats et al., 2007; Ehlers et al., 2007), but also by FRAP (Ashby et al., 2006; Sharma et al., 2006; Bats et al., 2007). The initial studies used latex particles coated with an antibody against the

extracellular domain of GluR2 (Borgdorff and Choquet, 2002) and were followed by single-molecule fluorescence imaging experiments [using organic dyes or semiconductor quantum dots; (Tardin et al., 2003; Groc et al., 2004; Bats et al., 2007; Ehlers et al., 2007)]. These experimental approaches showed that AMPARs diffuse rapidly in the extrasynaptic membrane, and a high proportion of mobile receptors are also detected inside synapses. Moreover, AMPARs enter and exit synapses through lateral diffusion, and this diffusion is regulated during protocols that modify receptor accumulation at synapses. Accordingly, FRAP studies in cultured hippocampal neurons showed that spine proteins, including EYFP-GluR1, undergo continual exchange with extrasynaptic pools (approximately 40% of total spine GluR1 exchanges with pools from the rest of the cell within 5 min). Stimulation of synaptic NMDA receptors under conditions that raise the strength of glutamatergic synapses increased the mobile fraction of receptors but a slower kinetics for spine GluR1 was observed (Sharma et al., 2006). Other FRAP and fluorescence loss in photobleaching (FLIP) studies in cultured hippocampal neurons expressing SEP-GluR2 unraveled a population of surface receptors that continually move in and out of the dendritic spine by lateral diffusion, and showed a barrier to AMPAR lateral movement located at the spine neck (Ashby et al., 2006).

A recent attempt to understand the mechanisms that regulate the lateral diffusion of AMPAR led to evidence that the exchange of AMPAR by lateral diffusion from extrasynaptic to synaptic sites depends on the interaction of Stargazin with PSD-95, since disruption of this interaction increases AMPAR surface diffusion and prevents AMPAR accumulation at synapses (Bats et al., 2007). Interestingly, local synaptic activity reduces the diffusional exchange of GluR1 between synaptic and extrasynaptic domains, resulting in postsynaptic accumulation of GluR1-containing AMPAR. In contrast, at neighbor inactive synapses GluR1 was found to be highly mobile (Ehlers et al., 2007), in agreement with an earlier study showing that synapse-specific silencing of neurotransmission causes a reduction in synaptic GluR1-containing AMPARs, in comparison to nearby active synapses (Harms et al., 2005).

Regulated AMPAR internalization is mediated by clathrin-dependent endocytosis (Beattie et al., 2000; Man et al., 2000), and requires the interaction between GluR2 and AP2, a clathrin adaptor protein (Lee et al., 2002). In cultured neurons, several stimuli can cause AMPAR internalization, such as the activation of NMDARs (Carroll et al., 1999; Beattie et al., 2000; Ehlers, 2000), AMPARs (Lin et al., 2000), mGluRs (Snyder et al., 2001; Xiao et al., 2001) or insulin receptors (Lin et al., 2000; Man et al., 2000). Receptor internalization may be caused by different signaling pathways, and AMPARs are differentially sorted between recycling and degradative pathways following endocytosis, depending on the endocytic stimulus (Ehlers, 2000; Lin et al., 2000). AMPAR internalization triggered by NMDAR activation is $Ca^{2+}$-dependent, requires protein phosphatase activity and dephosphorylation of GluR1, and is followed by rapid membrane reinsertion of AMPAR (Ehlers, 2000). AMPA-induced AMPAR endocytosis depends on the secondary activation of voltage-gated calcium channels, and is triggered also by ligand binding independent of receptor activation (Lin et al., 2000). AMPARs internalized in response to AMPA stimulation also enter a recycling endosome system (Lin et al., 2000).

Several studies have revealed the presence of specializations dedicated to endocytosis stably positioned adjacent to the postsynaptic membrane in dendritic spines (Blanpied et al., 2002; Petralia et al., 2003; Racz et al., 2004). These endocytic zones lie in lateral domains of the spine, and they develop and persist independent of synaptic activity (Blanpied et al., 2002). Recently, Lu et al. (2007a) reported evidences that provide a mechanistic explanation for the retention of the endocytic zones close to the PSD. Correct positioning of the endocytic zones requires association between dynamin 3, a postsynaptic GTPase with a role in severing the neck of invaginated clathrin-coated vesicles, and the postsynaptic adaptor Homer, which in turn binds to Shank. Synaptic localization of the endocytic zones was disrupted by overexpression of the proline-rich domain of dynamin 3, which inhibits the binding of wild-type dynamin 3 to Homer. Moreover, coupling of the endocytic zones to the postsynaptic densities requires oligomerization of dynamin 3, and is disrupted by loss of endogenous dynamin 3. Surprisingly, the localization of the endocytic machinery close to the postsynaptic densities was found to play an important role in maintaining synaptic AMPARs and in sustaining basal excitatory transmission. To account for these counterintuitive evidences, it was suggested that endocytic zones at close proximity to the PSD may capture AMPARs laterally while they are diffusing out of the PSD, and promote their recycling back to the synapse. This model suggests that the endocytic zones adjacent to the PSD provide the means for maintaining synaptic AMPARs. It remains to be determined whether this mechanism is somehow specific to AMPARs, or whether the endocytic zones peripheral from the PSD play a general role in removing membrane proteins in the edge of the PSD.

Interestingly, Ashby et al. (2004) used pHluorin-GluR2 expressed in hippocampal neurons in culture to follow NMDAR-dependent AMPAR endocytosis, and found that in synaptic regions GluR2 fluorescence slowly declines after the period of NMDA application, whereas extrasynaptic pHluorin-GluR2 fluorescence decreased sharply during NMDA application, suggesting rapid internalization of extrasynaptic AMPARs. These results suggest that NMDA-receptor triggered synaptic removal of AMPARs is preceded by endocytosis of extrasynaptic AMPARs, which could promote lateral diffusion of synaptic AMPARs out of the PSD. It would be interesting to investigate what happens to the endocytic zones adjacent to the PSD under these experimental conditions.

The *Arc*/*Arg3.1* immediate-early gene is regulated by neuronal activity. *Arc*/*Arg3.1* mRNA is transported to dendrites, and accumulates at sites of synaptic activity, where it is translated (Guzowski et al., 2005), conferring temporal and spatial specificity to the expression of the Arc/Arg3.1

protein. This protein interacts with dynamin 2 and with specific isoforms of endophilin, to localize to endosomes, and to enhance AMPAR endocytosis in hippocampal neurons (Chowdhury et al., 2006). In hippocampal neurons prepared from Arc/Arg3.1 knockout mice, receptor endocytosis is decreased, and the surface levels of AMPARs are upregulated, suggesting that the Arc/Arg3.1-regulated endocytic pathway modulates the basal level of AMPARs (Chowdhury et al., 2006). Another immediate-early gene, CPG2, a brain-specific splice variant of the syne-1 gene that encodes a protein specifically localized to the postsynaptic endocytotic zone of excitatory synapses, mediates both constitutive and regulated AMPAR endocytosis (Cottrell et al., 2004).

It is becoming more evident that exocytosis, lateral diffusion and endocytosis are key players in AMPAR trafficking. It still remains to be determined how these processes relate dynamically, to insert, retain and remove synaptic AMPARs. Further investigation in this field should reconcile the apparently contradictory evidences concerning the location and regulation of AMPAR surface delivery and removal.

## AMPAR PHOSPHORYLATION AND TRAFFICKING IN SYNAPTIC PLASTICITY

AMPARs play a key role in the expression of LTP and LTD, which are extensively investigated forms of synaptic plasticity, thought to underlie learning and memory formation (Martin et al., 2000; Morris, 2006). LTP is characterized by a persistent increase in the efficacy of synaptic transmission, following a short period of high-frequency synaptic stimulation [e.g. (Morris, 2006)]. Pharmacological stimulation of excitatory synapses also induces a long-term increase in synaptic activity, named chemical LTP [e.g. (Broutman and Baudry, 2001; Lu et al., 2001; Park et al., 2004)]. In contrast, a period of low-frequency synaptic stimulation reduces synaptic strength (LTD). Increasing evidence suggests that at many excitatory synapses, phosphorylation of AMPARs, and their insertion or removal from the PSD, underlie the changes in synaptic strength associated with LTP or LTD, respectively.

### Role of AMPARs in LTP

AMPARs present in the adult hippocampus contain GluR1 and GluR2, or GluR3 and GluR2 subunits (Wenthold et al., 1996). Several lines of evidence point to a central role of GluR1 in hippocampal LTP. Thus, GluR1$^{-/-}$ mice are deficient in LTP (Zamanillo et al., 1999), in contrast with the enhanced LTP observed in mice lacking GluR2 (Jia et al., 1996). Studies using hippocampal organotypic cultures transiently expressing GFP-tagged AMPAR subunits showed a rapid translocation of GluR1-GFP to dendritic spines following induction of LTP (Shi et al., 1999; Hayashi et al., 2000), which accounts, in part, for the increased response to synaptically released glutamate. The translocation of GluR1 to the membrane requires high-frequency stimulation of the synapse and is dependent on NMDA receptor activation (Shi et al., 1999). The same experimental approach showed that GluR2 subunits are constitutively delivered to synapses, in contrast with GluR1. The GluR1 regulatory mechanism is dominant, since heteromeric receptors containing GluR1 and GluR2 subunits behave like the GluR1 (Shi et al., 2001). *In vivo* studies also showed a reversible increase in GluR1 and GluR2 protein levels in synaptoneurosomes (a subcellular fraction containing the pre and postsynaptic components of the synapse) isolated from the hippocampal CA1 region subjected to high-frequency stimulation (Lu et al., 2001). Similarly, LTP induction in the dentate gyrus of awake adult rats also induce a rapid NMDA receptor-dependent increase in the surface expression of GluR1–GluR3 subunits, but GluR1 was the only AMPAR subunit with an increased expression in the post-synaptic density (Williams et al., 2007). Recent studies showed that LTP induces a rapid but transient increase in synaptic expression of GluR2-lacking $Ca^{2+}$-permeable AMPARs in 10 to 12-day-old mice. Although these receptors are subsequently replaced by GluR2-containing AMPARs, their transient expression in the synapse increases $Ca^{2+}$ permeability, and may contribute to the stabilization of LTP (Plant et al., 2006; Lu et al., 2007b). At later developmental stages GluR2-lacking AMPARs are no longer required for the early phase of LTP (Lu et al., 2007b), which may explain the discrepancies found in the literature concerning this issue (Adesnik and Nicoll, 2007; Gray et al., 2007).

Under resting conditions AMPARs are recycled in a constitutive manner between synapses and intracellular membrane compartments, where they are sorted for degradation or for reinsertion at synapses (Ehlers, 2000; Passafaro et al., 2001) (see above). The transport of GluR1-containing AMPARs to the plasma membrane from recycling endosomes is enhanced in response to LTP-inducing stimuli, thereby increasing synaptic efficacy (Broutman and Baudry, 2001; Park et al., 2004). The recycling pool of AMPARs has been shown to supply not only AMPARs but also lipid membrane for extension of dendritic spines during LTP (Park et al., 2004, 2006). The delivery of AMPARs to the synapse requires membrane fusion events, since inactivation of postsynaptic SNAREs with botulinum toxin reduces LTP induced by tetanic stimulation in the CA1 region of the hippocampus (Lledo et al., 1998). Similar studies where LTP was induced in cultured hippocampal neurons by stimulation of postsynaptic NMDA receptors with glycine also showed a tetanus toxin-sensitive (SNARE dependent) AMPAR insertion into synapses during LTP (Lu et al., 2001). A brief stimulation of $D_1$ dopamine receptors, which facilitates LTP in neurons of the prefrontal cortex, also led to the clustering of GluR1-containing AMPARs near but not within the PSD. In this model, activation of NMDA receptors is required to induce the synaptic localization of AMPARs (Sun et al., 2005). The C-terminal PDZ ligand of the GluR1 subunit plays a key role in the activity-dependent trafficking of AMPARs to spines (Piccini and Malinow, 2002) and synapses (Hayashi et al., 2000; Kim et al., 2001). A model was proposed according to which LTP activates CaMKII, which then phosphorylates GluR1 and a protein that binds to the PDZ domain of

GluR1 (Hayashi et al., 2000; Shi et al., 2001). However, the role of the PDZ binding domain in the trafficking of GluR1 is still controversial (Kim et al., 2005). A recent study showed the delivery of a recombinant cytosolic GluR1 C-terminal fragment to the PSD after induction of LTP, and synaptic incorporation of this construct was sufficient to allow spine enlargement (Kopec et al., 2007). Therefore, in addition to the functional role of GluR1 delivery to the synapse, to increase synaptic strength, it also plays a structural role, increasing spine size.

PSD-95 may also function in the anchoring of GluR1 containing AMPARs, since expression of this protein in hippocampal slice cultures upregulates the amount of GluR1 found in synapses and increases synaptic transmission, occluding LTP (Ehrlich and Malinow, 2004; Gerges et al., 2004). An enhancement of LTP is also observed in PSD-95 knockout mice (Migaud et al., 1998), and similar findings were reported in another deletion mutant of PSD-95 (Beique et al., 2006). This suggests that the activity-dependent delivery of AMPARs to the synapse during LTP may occur in the absence of PSD-95, and may be mediated, for example, by Stargazin, which binds both AMPARs and PSD-95 (Schnell et al., 2002).

Phosphorylation of both GluR1-Ser831 (Barria et al., 1997; Lee et al., 2000., 2003) and GluR1-Ser845 (Lee et al., 2000; Esteban et al., 2003a) were originally suggested to mediate LTP expression. The use of phosphospecific antibodies, which bind GluR1 only when phosphorylated on Ser831 or on Ser845, showed that both sites are phosphorylated upon induction of LTP in the CA1 region of the hippocampus (Lee et al., 2000). Interestingly, the specific phosphorylation site involved in the expression of LTP depends on the history of the synapse, since high-frequency stimulation of naive synapses or of previously depressed synapses increases the phosphorylation of Ser831 (CaMKII phosphorylation site) and Ser845 (PKA phosphorylation site), respectively (Lee et al., 2000). The studies using adult mice with knock-in mutations in the Ser831 and Ser845 GluR1 phosphorylation sites showed a substantial reduction in the expression of LTP in the hippocampal CA1 region, correlated with an impairment in the retention of rapidly acquired new learning, but LTP was not completely absent when compared with the wild-type animals (Lee et al., 2003). GluR1 phosphorylation at Ser831 is also observed in the hippocampus of rats subjected to contextual fear conditioning (Shukla et al., 2007). Recent studies showed that PKC also phosphorylates GluR1 at Ser818 (Boehm et al., 2006) and at Thr840 (Lee et al., 2007), being the former site crucial for LTP.

The mechanisms whereby phosphorylation of GluR1 contributes to LTP are still not fully elucidated. Postsynaptic expression of a constitutively active form of CaMKII in hippocampal slices enhances synaptic transmission and prevents further induction of LTP, suggesting that CaMKII and LTP upregulate synaptic transmission through the same mechanism (Pettit et al., 1994; Lledo et al., 1998). The effect of constitutively active CaMKII on synaptic delivery of GluR1 is abrogated by inhibition of PKA, but activation of PKA signaling independently is not enough to induce delivery of the receptors to the synapse (Esteban et al., 2003a). Also, activation of PKA signaling with forskolin and rolipram increases the amount of GluR1 associated with the plasma membrane in cultured hippocampal neurons, but no major changes in synaptic activity are observed under these conditions (Oh et al., 2006), suggesting that there is no delivery of AMPARs to the synapse. However, when PKA activity is associated with stimulation of synaptic NMDA receptors there is an increased incorporation of AMPARs into synapses, and induction of LTP (Oh et al., 2006). Taken together, these evidences suggest that GluR1 phosphorylation of Ser845 delivers AMPARs to the plasma membrane, being the influx of $Ca^{2+}$ through NMDA receptors necessary for the diffusion of the receptors until they reach the synapse, promoting synaptic potentiation (Oh et al., 2006). A recent study showed that GluR1 phosphorylation at Ser845 may also be accomplished by cGKII, which complements the PKA-induced surface increase of GluR1 (Serulle et al., 2007). The delivery of GluR1-containing AMPARs to the synapse and/or their stabilization in the synaptic compartment may also depend on the phosphorylation at Ser818 by PKC (Boehm et al., 2006) and on the CaMKII-dependent phosphorylation of a PDZ domain containing substrate that remains to be identified (Hayashi et al., 2000).

In addition to the effects on receptor trafficking, phosphorylation of GluR1 may also regulate its electrophysiological properties, contributing to synaptic potentiation. Thus, phosphorylation of GluR1 on Ser831 and Ser845 increases the apparent single-channel conductance (Derkach et al., 1999) and the apparent open-channel probability (Banke et al., 2000), respectively. However, under normal conditions GluR1 phosphorylation on Ser831 may not affect its electrophysiological properties, since a recent study showed no phosphorylation-induced increase in single AMPA channel properties when GluR1 is oligomerized with GluR2 (Oh and Derkach, 2005), which is the case in most native AMPARs (Wenthold et al., 1996).

The small GTPase Ras mediates the NMDA receptor and CaMKII signaling that drives synaptic accumulation of AMPAR subunits with long cytoplasmic tails during LTP (Zhu et al., 2002). Under resting conditions, the spontaneous neuronal activity contributes to low levels of Ras activity which are still sufficient to activate the Ras/ERK (extracellular signal-regulated kinase) signaling pathway, driving GluR2L to the synapse. An increase in neuronal activity further upregulates Ras, allowing the activation of the Ras-PI3-K signaling pathway, which drives GluR1 to synapses (Qin et al., 2005). It was suggested that the Ras/ERK and Ras–PI3-K pathways lead to synaptic delivery of GluR1 subunits by triggering the phosphorylation of Ser845 and Ser831 of GluR1, respectively, and the delivery of GluR2L is dependent on Ser842 phosphorylation induced by the former signaling pathway. A similar mechanism may be involved in the synaptic delivery of GluR1 subunits in hippocampal neurons exposed to BDNF (Caldeira et al., 2007), a neurotrophin that activates the Ras/ERK and the PI3-K signaling pathways in cultured hippocampal neurons (Almeida et al., 2005). Activation of the

Trk neurotrophin receptors by BDNF induces GluR1 phosphorylation on Ser831 (Caldeira et al., 2007), and plays a key role in LTP in the hippocampus [reviewed in (Carvalho et al., 2008)]. However, since it is very unlikely that ERK and PKB/Akt directly phosphorylate GluR1 or GluR2L, it remains to be determined which are the downstream signaling mechanisms involved. Also, the mechanisms involved in the regulation of Ras activity that are relevant to its effects in the regulation of AMPAR trafficking remain unknown. Rab8 is a distinct small GTPase that is also necessary for the synaptic delivery of GluR1-containing AMPARs induced by a constitutively active form of CaMKII, overexpression of PSD-95 and induction of LTP in cultured hippocampal slices (Gerges et al., 2004). Rab8 is present in both *trans*-Golgi network and recycling endosomes (Ang et al., 2003), but it was proposed that the effects of this small GTPase on LTP occur at the level of the former compartment (Gerges et al., 2004).

Several proteins of the PSD that interact with AMPARs have been shown to play a role in synaptic plasticity, by modulating the trafficking of the receptors. Overexpression of some of the proteins of the TARPs family leads to the accumulation of AMPARs in non-synaptic regions (Schnell et al., 2002; Rouach et al., 2005), in agreement with the two-step model for AMPAR trafficking in LTP. One of the TARPs, Stargazin ($\gamma$-2), is phosphorylated at the C-terminal region by CaMKII and PKC, and the phosphorylated protein enhances AMPAR activity. Phosphorylation of Stargazin is dynamically regulated by NMDA receptor activation, and inhibition of Stargazin phosphorylation disrupts the dynamic recruitment of AMPARs necessary for LTP (Tomita et al., 2005). The synaptic delivery of AMPARs induced by Stargazin phosphorylation also requires the Stargazin PSD-95 PDZ binding site (Tomita et al., 2005), but how phosphorylation of this TARP promotes synaptic trafficking is still unknown.

The presence of the molecular machinery necessary for translation activity in spines and dendritic shafts (Steward and Levy, 1982; Tang and Schuman, 2002; Asaki et al., 2003), and the observed translocation of polyribosomes from dendritic shafts to spines following tetanic stimulation, which also increases the number of spines that contain polyribosomes (Ostroff et al., 2002), suggest that local protein synthesis may play an important role in synaptic plasticity. Accordingly, an overall increase in protein synthesis was observed in experiments where patterned synaptic stimulation was paired with muscarinic receptor activation with carbachol, in hippocampal slices (Feig and Lipton, 1993). The mRNAs coding for AMPAR subunits are found in dendrites, suggesting that local synthesis of AMPAR subunits may determine the abundance of receptors and/or their composition (Kacharmina et al., 2000; Ju et al., 2004; Grooms et al., 2006). An elegant study using the arsenic-based dyes FlAsH and ReAsH showed that transfected tagged GluR1 and GluR2 subunits can be synthesized in a dendritic compartment independent from the cell body, in cultured hippocampal neurons (Ju et al., 2004). Studies using a protein synthesis reporter consisting of GFP flanked by the 5′ and 3′ untranslated regions from the CaMKII $\alpha$-subunit, which contains information sufficient for the dendritic localization of the mRNA, also showed that BDNF may induce dendritic protein synthesis (Aakalu et al., 2001). The neurotrophin BDNF plays an important role in synaptic plasticity (Carvalho et al., 2008), and studies in hyppocampal synaptoneurosomes showed that BDNF induces local synthesis of GluR1 (Schratt et al., 2004). Activation of $D_1$-type dopamine receptors also increases rapidly GluR1 protein synthesis and enhances the frequency of spontaneous mEPSCs in hippocampal neurons (Smith et al., 2005). However, it remains to be determined to what extent the local synthesis of AMPAR subunits contributes to LTP.

### Role of AMPARs in LTD

Low levels of synaptic stimulation can activate NMDARs to produce NMDAR-dependent LTD of glutamatergic synaptic transmission, or activate mGluRs, to produce mGluR-dependent LTD. The two forms of LTD are thought to result from internalization of surface AMPARs in both hippocampal pyramidal neurons and cerebellar Purkinje cells.

*Hippocampal LTD.* In the CA1 region of the hippocampus, two mechanistically distinct forms of LTD can be induced, by triggering the activation of NMDARs or of mGluRs (Oliet et al., 1997). Interestingly, the magnitude of NMDAR-dependent LTD in the CA1 area of the hippocampus correlates with cognitive performance in young rats, whereas the magnitude of NMDAR-independent LTD correlates favorably with cognitive outcome in aged rats (Lee et al., 2005).

NMDAR-dependent LTD in the CA1 region of the hippocampus is known to require a moderate increase in postsynaptic calcium (Cummings et al., 1996), activation of protein phosphatases (Mulkey et al., 1993, 1994), dephosphorylation of the GluR1 subunit of AMPARs (Lee et al., 2000, 2003), and AMPAR internalization (Beattie et al., 2000; Carroll et al., 2001). Regulated endocytosis of AMPARs requires the interaction between GluR2 and the clathrin adaptor protein AP2 (Lee et al., 2002). The neuronal calcium sensor hippocalcin binds the $\beta$2-adaptin subunit of the AP2 adaptor, in a calcium-sensitive manner, and infusion of a truncated mutant of hippocalcin, that lacks the calcium binding domains, prevents synaptically evoked LTD (Palmer et al., 2005a). These evidences suggest that the AP2-hippocalcin complex may act as a calcium sensor that couples NMDAR activation to regulated endocytosis of AMPARs during LTD. Additionally, a recent study shows that bath application of NMDA for a short period to hippocampal neurons in culture, a protocol used to induce chemical LTD, causes a dramatic decrease in the phosphorylation of PSD-95 on Ser295, and overexpression of the phosphomimicking Ser295Asp mutant of PSD95 blocks AMPAR internalization and LTD (Kim et al., 2007).

There are evidences leading to conflicting models regarding the role of GluR2 phosphorylation at Ser880, and GluR2 interaction with PICK1 and GRIP/ABP, in hippocampal LTD. Perez et al. (2001) found evidences that, similar to what has been found concerning cerebellar LTD

(see below), disruption of the GluR2-GRIP1/ABP interaction by GluR2 phosphorylation results in the removal of synaptic receptors, by facilitation of the GluR2–PICK1 interactions. This model is further supported by a study in hippocampal slice cultures, where mimicking GluR2 Ser880 phosphorylation was found to exclude receptors from synapses, to depress transmission and to partially occlude LTD (Seidenman et al., 2003), and by a study showing that a Bin/amphyphysin/Rvs (BAR) domain mutant of PICK, unable to bind lipids, impairs expression of LTD in hippocampal neurons (Jin et al., 2006). On the other hand, Daw et al. (2000) reported that Ser880 phosphorylation can reverse LTD, by disrupting the intracellular retention of GluR2 by GRIP/ABP, and allowing receptors to be delivered to the synapse. The recent study by Lin and Huganir (2007) indicates that the binding of PICK1 to GluR2 regulates intracellular pools of GluR2 in recycling endosomes, that may be regulated differentially in response to different signaling pathways.

NMDAR-dependent LTD induction produces a rapid and transient increase of the active, GTP-bound, small GTPase Rab5, which drives the specific internalization of synaptic AMPARs in a clathrin-dependent manner, and is required for hippocampal LTD (Brown et al., 2005). In addition, there are evidences that the Rap1-p38 MAPK pathway is also involved in the NMDAR-dependent LTD in CA1 synapses (Zhu et al., 2002).

Arc/Arg3.1 is an immediate early gene which expression is increased by neuronal activity, and which is specifically targeted to stimulated synaptic areas. Arc has recently been found to reduce AMPAR-mediated currents, by endocytic removal of AMPAR composed of GluR2/GluR3, and Arc overexpression occludes NMDAR-dependent hippocampal LTD (Rial Verde et al., 2006). Accordingly, hippocampal LTD is significantly impaired in *Arc/Arg3.1* knockout mice, and these mice fail to form long-lasting memories (Plath et al., 2006).

mGluR-mediated LTD at CA1 synapses in the hippocampus can be induced by agonists selective for group I mGluRs (Palmer et al., 1997), relies on dendritic protein synthesis (Huber et al., 2000), and involves activation of MAPKs (Gallagher et al., 2004; Huang et al., 2004) and protein tyrosine phosphatases (Moult et al., 2002). mGluR-induced LTD is associated with a decrease of surface GluR1 AMPAR clusters (Snyder et al., 2001), and with tyrosine dephosphorylation of GluR2 AMPAR subunit (Moult et al., 2006).

Interestingly, beta-amyloid (A$\beta$), the peptide generated from the amyloid precursor protein and which is believed to underlie the pathophysiology of Alzheimer's disease, drives the loss of cell surface AMPARs from CA1 hippocampal pyramidal neurons, employing signaling pathways of LTD (Hsieh et al., 2006). In fact, A$\beta$-induced synaptic depression partially mimics and occludes mGluR-dependent LTD, and AMPAR endocytosis is required for A$\beta$-induced synaptic depression.

*Cerebellar LTD.* Cerebellar LTD corresponds to a persistent decrease in synaptic strength at the parallel fiber-Purkinje cell synapses, which is thought to be critical for some types of motor learning, and which is induced by coincident repeated activation of parallel fiber and climbing fiber inputs to Purkinje cells (Ito, 2001, 2002). The simultaneous activation of AMPARs, mGluRs and voltage-gated calcium channels on postsynaptic Purkinje cells induces cerebellar LTD (Ito, 2001, 2002), by raising the postsynaptic calcium concentration and activating PKC.

Expression of cerebellar LTD requires clathrin-mediated endocytosis (Wang and Linden, 2000), presumably of AMPARs, following GluR2 phosphorylation at Ser880 by PKC (Chung et al., 2003). In fact, LTD was absent in cultured cerebellar Purkinje cells from mutant mice lacking GluR2 and could be rescued by transient transfection with the wild-type GluR2 subunit. Transfection with a point mutant that eliminated PKC phosphorylation of Ser880 in the carboxy-terminal PDZ ligand of GluR2 failed to restore LTD. In contrast, transfection with a point mutant that mimicked phosphorylation at Ser880 occluded subsequent LTD (Chung et al., 2003). PKC phosphorylation of the AMPAR GluR2 subunit differentially modulates its interaction with the PDZ domain-containing proteins GRIP1 and PICK1. Phosphorylation of Ser880 in the GluR2 PDZ ligand decreases GluR2 binding to GRIP1 but not to PICK1 (Matsuda et al., 1999; Chung et al., 2000). By disrupting the interaction of GluR2 with GRIP1, Ser880 phosphorylation by PKC promotes GluR2 binding to PICK1, and PICK1-mediated internalization of AMPARs during LTP (Chung et al., 2000; Perez et al., 2001; Chung et al., 2003). A recent study shows that targeted *in vivo* mutation of PICK1 eliminates cerebellar LTD, which can be rescued in cerebellar cultures from mice lacking PICK1 by transfection of wild-type PICK1, but not of a PDZ mutant of PICK1 or of a mutant lacking the lipid-binding BAR domain (Steinberg et al., 2006), a protein module of about 200 amino acids, frequently found in proteins involved in membrane trafficking. PICK1 has also been shown to bind calcium ions, and the PICK1–GluR2 interaction in neurons is calcium-sensitive, with weak binding at zero calcium, stronger binding at $\sim$15 $\mu$M of intracellular calcium, and low binging at higher calcium concentrations (Hanley and Henley, 2005). This would allow PICK1 to respond to a local low-micromolar concentration of calcium, to bind GluR2 and initiate AMPAR endocytosis. In the presence of a large calcium signal, the affinity of PICK1 for GluR2 would be decreased. PICK1 may thus play a role in distinguishing between the calcium signals involved in LTP and LTD.

LTD of the parallel fiber (PF) –Purkinje cell synapses also requires the participation of $\delta$2 glutamate receptors (GluR$\delta$2), which are predominantly expressed postsynaptically (Landsend et al., 1997). This form of plasticity is thought to underlie motor coordination and information storage (Ito, 1989; Hansel et al., 2001; Ito, 2001), but the molecular mechanisms involved are still not fully understood. This is in part due to limited current understanding about the signaling activity of these receptors. Although GluR$\delta$2 has been considered as a subunit of ionotropic glutamate receptors, they were never shown to bind glutamate, or to be incorporated into native ionotropic gluta-

mate receptors [reviewed in (Yuzaki, 2003)]. Furthermore, GluR$\delta$2 do not contribute to normal excitatory postsynaptic currents (Kano and Kato, 1987) and a recent study suggested a non-ionotropic receptor function of GluR$\delta$2 in the control of cerebellar synaptic plasticity (Kakegawa et al., 2007). Several lines of evidence suggest that these subunits play an important role in parallel fiber–Purkinje cell LTD. The induction of LTD is abrogated when the expression of GluR$\delta$2 is knocked down using antisense oligonulceotides (Hirano et al., 1994; Jeromin et al., 1996) or in knockout mice (Hirano et al., 1995; Kashiwabuchi et al., 1995), and exogenous expression of the receptors in knockout Purkinje neurons or knockout mice rescues LTD induction (Hirai et al., 2005; Hirano, 2006). An antibody against the LAOBP (lysine-arginine-ornitine-binding protein) -like extracellular domain of GluR$\delta$2 induces an LTD-like response in cultured Purkinje neurons, and the same experimental strategy leads to internalization of AMPARs, reduces parallel fiber–Purkinje cell synaptic transmission and abolishes LTD (Hirai et al., 2003). The analysis of the PDZ proteins that interact with GluR$\delta$2, including nPIST (Yue et al., 2002), PSD-93 (Roche et al., 1999), PTPMEH (Hironaka et al., 2000), shank (Uemura et al., 2004), delphilin (Miyagi et al., 2002) and SCAM/MAGI-2 (Yap et al., 2003a), and other interactors lacking PDZ domains, including spectrin (Hirai and Matsuda, 1999), AP4 (Yap et al., 2003b) and the microtubule-associated protein EMAP (Ly et al., 2002), may provide clues about the regulation of the trafficking and function of this receptor. Interestingly, a recent study showed an attenuation of LTD at the parallel fiber–Purkinje cell synapses in PTPMEH-knockout mice (Kina et al., 2007).

## AMPARs IN HOMEOSTATIC PLASTICITY

Homeostatic synaptic scaling complements the Hebbian forms of plasticity (LTP and LTD), stabilizing the activity of a neuron by scaling up or down the strength of all synapses, proportionally to their initial strength (Turrigiano, 2007). Without any stabilizing mechanisms, LTP and LTD would lead neuronal activity to excessive excitation or to quiescence, respectively. Synaptic scaling provides the negative feedback to maintain neuronal activity within a functional range.

This form of plasticity acts through synergistic presynaptic and postsynaptic changes (Turrigiano, 2007). We will review here how changes in postsynaptic AMPAR accumulation contribute to synaptic scaling of excitatory synapses. Chronic manipulations of neuronal activity in dissociated cultured neurons produce effects on the number of synaptic AMPARs, and on AMPAR-mediated excitatory postsynaptic currents (Lissin et al., 1998; O'Brien et al., 1998; Turrigiano et al., 1998). Increasing activity by chronically blocking inhibitory synaptic transmission using picrotoxin leads to a decrease in the number of surface AMPARs in hippocampal (Lissin et al., 1998), spinal (O'Brien et al., 1998) or cortical (Turrigiano et al., 1998) neurons in culture. On the other hand, chronic application of the glutamate receptor antagonists CNQX and APV to cultured spinal cord neurons caused an increase in the surface expression of AMPARs at synapses, and in the amplitude of AMPAR-mediated mEPSCs (O'Brien et al., 1998), and chronic blockade of AMPARs in cultured hippocampal neurons increased the number, size and fluorescent intensity of AMPAR clusters and rapidly induced the appearance of AMPARs at silent synapses (Liao et al., 1999).

Several activity-dependent molecular signals have been implicated in the molecular mechanisms underlying synaptic scaling. Secreted factors such as BDNF and the proinflammatory cytokine tumor necrosis factor-$\alpha$ (TNF$\alpha$), as well as the immediate early gene product Arc, have been proposed to play a role in synaptic scaling (Turrigiano, 2007). Chronic BDNF treatment of cortical cultures can overcome the effect of chronic synaptic activity blockade (Rutherford et al., 1998), and TNF$\alpha$, secreted from glia cells, appears to be necessary for the increase in the level of synaptic AMPARs caused by long periods of activity blockade using TTX, a voltage-gated sodium channel blocker (Stellwagen and Malenka, 2006). The fact that a factor released by glia cells is required for synaptic scaling indicates that network, rather than cell-autonomous, changes in activity are implicated in the form of synaptic scaling mediated by TNF$\alpha$. The expression of the immediate early gene *Arc* is regulated by the chronic manipulations of activity in culture which are used to induce synaptic scaling, with high activity inducing high levels of Arc protein and activity blockade decreasing Arc protein levels. Moreover, overexpression of Arc blocks the homeostatic increases in AMPAR function induced by chronic activity blockade in culture (Shepherd et al., 2006), in agreement with the role of Arc in AMPAR endocytosis (Chowdhury et al., 2006), and hippocampal neurons from Arc KO mice show no synaptic scaling (Shepherd et al., 2006). The relative role of BDNF, TNF$\alpha$ and Arc in signaling changes in activity to induce or modulate synaptic scaling is still unclear.

Importantly, synaptic scaling was observed *in vivo* in cortical synapses following sensory deprivation (Desai et al., 2002; Goel et al., 2006). In the visual cortex, 1 week of dark rearing resulted in an increase in the ration of GluR1 to GluR2 in the postsynaptic densities. Conversly, in the somatosensory cortex, dark rearing decreased the GluR1/GluR2 ratio (Goel et al., 2006). These evidences suggest that manipulation of visual experience regulates not only synaptic AMPARs in the visual cortex, but also results in complementary changes in the somatosensory cortex, and indicate that the regulation of AMPARs is a downstream mechanism for homeostatic plasticity *in vivo*.

## CONCLUSION

The recent advances in the study of the molecular mechanisms of regulation of AMPARs have contributed, to a great extent, to the understanding of synaptic plasticity. Future studies concerning the signaling mechanisms governing AMPAR trafficking, the direct/indirect interaction of AMPAR subunits with intracellular proteins, and the spatial

distribution of the receptor trafficking will contribute to a better understanding of LTP and LTD. In particular, the recent development of molecular imaging tools may allow determining how receptor exocytosis, lateral diffusion and endocytosis relate dynamically, to insert, retain and remove synaptic AMPARs during synaptic plasticity. Furthermore, the presence of the molecular machinery required for the synthesis of AMPAR subunits in dendrites suggests that local translation may play a regulatory role of AMPAR properties and trafficking.

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