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REVIEW

Intracellular machinery for the transport of AMPA receptors

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AMPA-type glutamate receptors are one of the most dynamic components of excitatory synapses. Their regulated addition and removal from synapses leads to long-lasting forms of synaptic plasticity, known as long-term potentiation (LTP) and long-term depression (LTD). In addition, AMPA receptors reach their synaptic targets after a complicated journey involving multiple transport steps through different membrane compartments. This review summarizes our current knowledge of the trafficking pathways of AMPARs and their relation to synaptic function and plasticity.
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Abbreviations: ABP, AMPA receptor-binding protein; AMPA, γ-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; ER, endoplasmic reticulum; GRIP1, glutamate receptor-interacting protein 1; LTD, long-term depression; LTP, long-term potentiation; MAGUK, membrane-associated guanylate kinase; NMDA, N-methyl-D-aspartate; NSF, N-ethyl-maleimide-sensitive factor; PDZ, PSD95/Discs-Large/ZO-1; PICK1, protein interacting with C-kinase 1; PSD, postsynaptic density; SAP97, synapse-associated protein 97; TARP, transmembrane AMPAR regulatory protein

Introduction

Intracellular membrane trafficking is an essential process in all eukaryotic cells, but it is particularly critical at synaptic terminals, where a large number of specific ion channels, scaffolding molecules and multiple signal transduction regulators have to be precisely targeted to ensure proper synaptic function (McGee and Bredt, 2003; Ziv and Garner, 2004). At the level of the postsynaptic terminal, local membrane trafficking is now appreciated as major factor controlling synaptic function (Kennedy and Ehlers, 2006). In particular, the regulation of neurotransmitter receptor transport and targeting is crucial for the maintenance of synaptic strength, and for the activity-dependent changes associated to synaptic plasticity (Collingridge *et al*., 2004).

Three types of ionotropic (ion-channel type) glutamate receptors are present at excitatory synapses in the brain: γ-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), N-methyl-D-aspartate (NMDA) and kainate receptors. AMPA and NMDA receptors (NMDARs) are responsible for most excitatory transmission in CNS (Hollmann and Heinemann, 1994; Dingledine *et al*., 1999), whereas kainate receptors play important roles in the modulation and plasticity of the synaptic response (Lerma, 2006). AMPA receptors (AMPARs) mediate fast excitatory (depolarizing) currents in conditions of basal neuronal activity, and hence, they have a major influence in the strength of the synaptic response. NMDARs, on the other hand, remain silent at resting membrane potential (Nowak *et al*., 1984), but they are crucial for the induction of specific forms of synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD) (Bear and Malenka, 1994). Although AMPARs and NMDARs reside in the same synapses in most brain regions, they reach their synaptic targets through quite different programs. In the brain, soon after birth, most excitatory synapses in the hippocampus (Durand *et al*., 1996; Hsia *et al*., 1998; Petralia *et al*., 1999) and other brain regions (Wu *et al*., 1996; Isaac *et al*., 1997; Feldman *et al*., 1999; Losi *et al*., 2002) contain only NMDARs, whereas the prevalence of AMPARs increases gradually over the course of postnatal development. In fact, the delivery of AMPARs into synapses is a regulated process that depends on NMDAR activation and underlies some forms of synaptic plasticity in early postnatal development (Zhu *et al*., 2000) and in mature neurons (Hayashi *et al*., 2000; Sheng and Lee, 2001; Barry and Ziff, 2002; Malinow and Malenka, 2002; Song and Huganir, 2002).

Synaptic plasticity is thought to underlie higher cognitive functions, such as learning and memory (Hebb, 1949; Bliss

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and Collingridge, 1993; Chen and Tonegawa, 1997; Elgersma and Silva, 1999; Martin *et al*., 2000), and is also critical for neural development (Constantine-Paton, 1990; Katz and Shatz, 1996; Cline, 1998). Thus, it is not surprising that alterations in synaptic plasticity have been implicated in the pathology of several neurological disorders, including Alzheimer's disease (Rowan *et al*., 2003; Turner *et al*., 2003; Esteban, 2004), schizophrenia (Konradi and Heckers, 2003; Stephan *et al*., 2006), Down's syndrome (Galdzicki and Siarey, 2003) and other forms of mental retardation (Newey *et al*., 2005). Consequently, there is considerable interest in understanding the underlying mechanisms of synaptic plasticity, among which the regulation of AMPAR trafficking plays a prominent role.

This review will summarize our current knowledge of the membrane trafficking pathways that steer AMPARs from their biosynthesis at the endoplasmic reticulum (ER) to their destination at excitatory synapses, with special emphasis on the regulatory steps that contribute to synaptic plasticity. Most of the experimental observations that are the basis for this chapter have been obtained from hippocampal principal neurons, although it is expected that most of the principles described here will be applicable for the regulation of AMPAR trafficking in multiple brain regions.

AMPA receptor assembly and exit from the endoplasmic reticulum

AMPA receptors are hetero-tetramers (Rosenmund *et al*., 1998) composed of different combinations of GluR1, GluR2, GluR3 and GluR4 subunits (Hollmann and Heinemann, 1994). In the mature hippocampus, most AMPARs are composed of GluR1–GluR2 or GluR2–GluR3 combinations (Wenthold *et al*., 1996), whereas GluR4-containing AMPARs are expressed mainly in early postnatal development (Zhu *et al*., 2000). These oligomeric combinations are formed in the ER, possibly assembling as dimers of dimers (Tichelaar *et al*., 2004) via interactions between the luminal, N-terminal domains of the subunits (Kuusinen *et al*., 1999; Leuschner and Hoch, 1999; Greger *et al*., 2007). After assembly, exit from the ER is tightly regulated by quality control mechanisms that monitor the competency of newly synthesized receptors for ligand binding and gating (Fleck, 2006).

Interestingly, AMPAR trafficking through the ER is subunit-specific. Thus, GluR1–GluR2 hetero-oligomers exit the ER rapidly, and traffic to the Golgi compartment where they become fully glycosylated (Greger *et al*., 2002). In contrast, GluR2–GluR3 heteromers take much longer to exit (that is, are retained longer in) the ER. In fact, a fraction of the GluR2 subunits seems to remain unassembled within the ER, in a manner that depends on the presence of an edited arginine residue (R607) at the channel pore region (Greger *et al*., 2002, 2003). These immature AMPAR subunits appear to associate with molecular chaperones residing at the ER (Greger *et al*., 2002; Fukata *et al*., 2005). Interactions with cytosolic proteins also seem to control trafficking through the ER. For example, the GluR2 C terminus has a PSD-95/Discs-Large/ZO-1 (PDZ) consensus motif (-SVKI) that interacts with the PDZ domain-containing protein interacting with C-kinase 1 (PICK1) (Dev *et al*., 1999; Xia *et al*., 1999; Perez *et al*., 2001). This interaction is required for GluR2's exit from the ER (Greger *et al*., 2002).

In addition, export of AMPARs from the ER and surface expression is also facilitated by direct interaction with a family of 'transmembrane AMPAR regulatory proteins' (TARPs) (Vandenberghe *et al*., 2005; Ziff, 2007). In fact, TARPs may well be considered auxiliary subunits of AMPARs (Fukata *et al*., 2005), which assist in their proper folding and affect channel kinetics (Priel *et al*., 2005; Tomita *et al*., 2005; Turetsky *et al*., 2005; Bedoukian *et al*., 2006) and rectification properties (Soto *et al*., 2007). Interestingly, the modulatory role of TARPs on AMPAR function depends on the specific combination of AMPAR subunits and TARP family member (Cho *et al*., 2007; Kott *et al*., 2007; Milstein *et al*., 2007).

AMPA receptor trafficking along the microtubular cytoskeleton in dendrites

Although the dendritic synthesis of AMPARs has been recently reported (Ju *et al*., 2004), most receptors are likely to be synthesized in the neuronal body. Therefore, newly synthesized receptors will have to travel long distances from their point of biosynthesis to their final synaptic targets. The long-range dendritic transport of AMPARs is likely to depend on the microtubular cytoskeleton that runs along dendritic shafts. The transport of membrane organelles on microtubule tracks is an active process powered mainly by motor proteins of the kinesin and dynein superfamilies (Goldstein and Yang, 2000). Therefore, membrane compartments bearing AMPARs are likely to be recognized and transported by some of these motor proteins. The molecular mechanisms underlying these processes are still being elucidated.

The PDZ domain-containing protein glutamate receptor-interacting protein 1 (GRIP1) interacts directly with the heavy chain of conventional kinesin, as revealed by yeast two-hybrid screening (Setou *et al*., 2002). GRIP binds to the C-terminal PDZ motif of GluR2 and GluR3 (Dong *et al*., 1997; Srivastava *et al*., 1998), and hence, may serve as the link between AMPARs and microtubular motor proteins. In fact, the ternary complex formed by GluR2, GRIP1 and kinesin can be immunoprecipitated from brain lysates, and dominant-negative versions of kinesin reduce the presence of AMPAR at synapses (Setou *et al*., 2002).

AMPA receptors have also been shown to associate with a different neuron-specific kinesin motor, KIF1 (Shin *et al*., 2003). In this case, the adaptor molecule seems to be liprin-α, which interacts with GluR2–GRIP (Wyszynski *et al*., 2002) and with KIF1 (Shin *et al*., 2003). Another member of the liprin-α–AMPAR–GRIP complex is GIT1, which is also involved in AMPAR trafficking (Ko *et al*., 2003). Therefore, it seems that the GRIP1–AMPAR complex can be transported along dendrites by more than one type of kinesin motor.

In addition to this microtubular-dependent transport, it has recently been reported that the export of AMPARs from the cell body into the dendritic surface is powered by a specific actin-based motor protein, myosin Vb (Lise *et al*., 2006). Interestingly, this transport system was specific for the GluR1 subunit, and required the small GTPase Rab11, possibly acting as a linker between the motor protein and its membrane cargo. From these combined studies, it seems

likely that multiple links between AMPARs and cytoskeletal motor proteins will be discovered in the future, possibly mediated by specific scaffolding molecules.

Actin-dependent trafficking in spines

Most excitatory synapses in the adult brain occur on small dendritic protuberances called spines (Hering and Sheng, 2001). Dendritic spines lack microtubular cytoskeleton, but they are rich in highly motile actin filaments (Fischer *et al*., 1998). Therefore, at some point, AMPAR-containing organelles, trafficking along microtubular tracks, must be transferred to the actin-based cytoskeleton for their final delivery into synapses. The importance of the actin cytoskeleton for local AMPAR trafficking is underscored by the observation that pharmacological depolymerization of actin filaments leads to the removal of AMPARs from dendritic spines (Allison *et al*., 1998) and from synapses (Kim and Lisman, 1999).

The molecular mechanisms that may mediate the actin-based movement of AMPARs are largely unknown. Nevertheless, AMPARs can be linked to the actin cytoskeleton through several scaffolding proteins, such as 4.1N (Shen *et al*., 2000) and RIL (Schulz *et al*., 2004). The different members of the protein 4.1 family are known to couple the spectrin–actin cytoskeleton to different membrane-associated proteins (Hoover and Bryant, 2000). In particular, the neuronal isoform 4.1N interacts directly with GluR1 (Shen *et al*., 2000) and GluR4 (Coleman *et al*., 2003) through the juxtamembrane region of their cytoplasmic C-terminal tails. The other potential actin linker for AMPARs, RIL, is a multi-functional protein that interacts with an internal region of the GluR1 C terminus through its LIM domain, and with α-actinin through its PDZ domain. Interestingly, only AMPAR subunits with long C tails (GluR1 and GluR4) have been shown so far to couple with the actin cytoskeleton. Since these long-tail subunits are the ones involved in regulated (activity-dependent) delivery at the synapse (Malinow *et al*., 2000), it is tempting to speculate that actin-dependent transport may be particularly critical for AMPAR insertion into synapses during plasticity.

The transport of AMPARs along the spine–actin cytoskeleton is likely to be bidirectional, since AMPARs are known to move in and out of synapses in a very dynamic manner. This expectation has been recently confirmed by the identification of an actin-based motor protein, myosin VI, as a mediator of the endocytic removal of AMPARs from synapses (Osterweil *et al*., 2005). Myosin VI interacts with the GluR1-binding protein SAP97 (synapse-associated protein 97) (Wu *et al*., 2002), providing a mechanistic link between AMPARs (again through a long-tail subunit) and the motor protein that drives their internalization. Undoubtedly, further studies will be required to unravel what is likely to be a network of interactions mediating the transport of AMPARs along the actin cytoskeleton in synapses.

TARPs and AMPA receptor surface trafficking

Transmembrane AMPAR regulatory proteins are the only known transmembrane proteins found to be associated with AMPARs. The first TARP to be identified was stargazin, which was found as a spontaneous mutation in the stargazer mouse (Letts *et al*., 1998) and is critically required for cell surface expression of AMPARs in cerebellar granule cells (Chen *et al*., 2000). By sequence and structural homology, stargazin belongs to a large group of proteins that includes γ-subunits of Ca^{2+} channels and the claudin family of cell-adhesion molecules. Nevertheless, only five of these proteins have been described to bind AMPARs and affect their trafficking: stargazin, γ-3, γ-4, γ-8 (Tomita *et al*., 2003) and, more recently, γ-7 (Kato *et al*., 2007). Therefore, these are the proteins collectively known as TARPs. Interestingly, different TARPs display specific expression patterns in brain, which are to some extent complementary (Tomita *et al*., 2003).

Transmembrane AMPAR regulatory proteins associate with AMPARs early in their biosynthetic pathway, as mentioned above, and are able to combine with all AMPAR populations irrespective of their subunit composition (Tomita *et al*., 2003). The most striking property of TARPs is their critical role in the expression of AMPARs at the extrasynaptic neuronal surface. Genetic ablation of stargazin, the TARP member most abundantly expressed in cerebellum, results in a virtual depletion of AMPARs from the extrasynaptic surface in granule cells (Chen *et al*., 2000). Similarly, removal of γ-8, a TARP member that is almost exclusively expressed in hippocampus, precludes AMPAR surface expression in hippocampal pyramidal neurons (Rouach *et al*., 2005). Interestingly, TARPs seem to be a limiting factor for AMPAR cell surface delivery, since overexpression of the appropriate neuron-specific TARP leads to a marked increase in the number of AMPARs expressed on the plasma membrane (Chen *et al*., 2000; Rouach *et al*., 2005). The role of these extrasynaptic surface receptors is still debated, although morphological evidence indicates that they are highly mobile and can reach the postsynaptic membrane through lateral diffusion (Borgdorff and Choquet, 2002; Choquet and Triller, 2003; Tardin *et al*., 2003; Groc *et al*., 2004).

Transmembrane AMPAR regulatory proteins also participate in the trafficking of AMPARs into the synaptic membrane. TARPs contain a PDZ consensus sequence at the C terminus, which can bind the PDZ domain of membrane-associated guanylate kinase (MAGUK) proteins, such as postsynaptic density proteins 95 and 93 (PSD95 and PSD93) (Chen *et al*., 2000). MAGUKs are synaptic scaffolding molecules, which have been shown to be critical regulators of AMPAR delivery and/or stabilization at synapses (El-Husseini *et al*., 2000; El-Husseini Ael *et al*., 2002; Elias *et al*., 2006; Schluter *et al*., 2006). Therefore, TARPs are thought to be the molecular linkers between AMPARs and MAGUKs. In particular, the association between TARPs and MAGUKs has been recently shown to be critical to retain AMPARs at synapses. Thus, impairment of the PDZ interaction between stargazin (TARP) and PSD95 (MAGUK) leads to increased receptor diffusion out of the synaptic membrane (Bats *et al*., 2007). Therefore, a major function of the TARP–MAGUK interaction appears to be the stabilization/anchoring of AMPARs at synapses.

The dual role of TARPs in extrasynaptic surface expression and in receptor stabilization at synapses has led to the hypothesis that AMPAR synaptic delivery occurs in two

steps: insertion in the extrasynaptic surface followed by lateral diffusion and synaptic trapping. Indeed, there are morphological (Passafaro *et al*., 2001) and electrophysiological (Adesnik *et al*., 2005) observations supporting this scenario. However, there are also indications that extrasynaptic surface receptors are not a necessary source for synaptic delivery. For example, genetic ablation of the hippocampal TARP (γ-8) produced a virtual depletion of extrasynaptic AMPARs, with only a modest effect on the accumulation of AMPARs at synapses (Rouach *et al*., 2005). Conversely, TARP overexpression produces a massive increase in extrasynaptic AMPARs without any detectable effect on AMPAR-mediated synaptic transmission (Schnell *et al*., 2002; Rouach *et al*., 2005).

Clearly, more work will be required to decipher the anatomical details of AMPAR synaptic trafficking. It is also worth keeping in mind that the precise mechanism of AMPAR delivery may vary among different synapse types and developmental stages.

Subunit specificity for constitutive and regulated synaptic delivery of AMPA receptors

It is now well established that the final steps in the synaptic trafficking of AMPARs depend on their subunit composition, and specifically, on *cis* signals contained within their cytosolic C termini (Passafaro *et al*., 2001; Shi *et al*., 2001). In hippocampus, hetero-tetramers formed by GluR1–GluR2 and GluR2–GluR3 subunits, together with a smaller contribution from GluR1 homomers, represent the most common combinations in excitatory synapses (Wenthold *et al*., 1996). On the basis of experiments expressing recombinant AMPAR subunits in hippocampal neurons, it has been shown that GluR2–GluR3 hetero-tetramers continuously cycle in and out of synapses in a manner largely independent of synaptic activity (Passafaro *et al*., 2001; Shi *et al*., 2001). This process (constitutive pathway) preserves the total number of receptor at synapses, and therefore, it has been proposed to help maintaining synaptic strength in the face of protein turnover (Malinow *et al*., 2000). This constitutive cycling is very fast (half-time of minutes) and it requires a direct interaction between GluR2 and *N*-ethyl-maleimide-sensitive factor (NSF) (Nishimune *et al*., 1998). The precise role of NSF in this trafficking pathway is not fully understood yet. NSF assists in the dissociation of GluR2 from the PDZ domain protein PICK1 (Hanley *et al*., 2002). The disassembly of the GluR2–PICK1 complex may be required for AMPARs to cycle back into synapses or, alternatively, it may prevent PICK1-driven endocytosis. The continuous synaptic cycling of AMPARs also requires the molecular chaperon Hsp90 (Gerges *et al*., 2004b), although the mechanistic link between AMPARs and Hsp90 has not been elucidated yet.

In contrast with this constitutive trafficking, AMPARs containing GluR1 (Hayashi *et al*., 2000), GluR2-long (Kolleker *et al*., 2003) (a splice variant of GluR2; Kohler *et al*., 1994) or GluR4 (Zhu *et al*., 2000) are added into synapses in an activity-dependent manner during synaptic plasticity (AMPAR removal from synapses can also be regulated by activity, as discussed below). The regulated insertion of receptors is triggered transiently upon induction of LTP, and results in a net increase in the number of AMPARs present at synapses (Malinow *et al*., 2000). The synaptic delivery of GluR1 is also regulated by physiological stimulation in living animals, as it has been reported for neocortical neurons upon sensory stimulation (Takahashi *et al*., 2003), and in the lateral amygdala after fear conditioning (Rumpel *et al*., 2005). The subunit composition of the endogenous AMPARs that participate in regulated synaptic delivery has been more difficult to establish. Thus, both GluR2-lacking receptors (presumably GluR1 homomers) (Plant *et al*., 2006) and GluR2-containing receptors (presumably GluR1–GluR2 heteromers) (Bagal *et al*., 2005; Adesnik and Nicoll, 2007) have been proposed to be rapidly inserted into synapses upon NMDAR activation in hippocampal slices. Although the details remain to be clarified, the importance of subunit composition for the regulation of synaptic delivery is well established. This has been recently corroborated by *in vivo* studies, which demonstrated that sensory stimulation (Clem and Barth, 2006) or deprivation (Goel *et al*., 2006), as well as cocaine administration (Bellone and Luscher, 2006), can alter the prevalence of AMPARs with different subunit assemblies at synapses.

The activity-dependent synaptic delivery of AMPARs is regulated by several protein kinases, such as CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II) (reviewed in Lisman and Zhabotinsky, 2001), PKA (Ehlers, 2000; Esteban *et al*., 2003; Gomes *et al*., 2004; Gao *et al*., 2006; Man *et al*., 2007), PKC (Boehm *et al*., 2006; Ling *et al*., 2006; Gomes *et al*., 2007) and phosphatidylinositol 3 kinase (Man *et al*., 2003). Interestingly, the signalling cascades controlling the delivery of AMPARs to synapses, as well as the AMPAR subunits involved, change during development. Thus, early in postnatal development of the hippocampus, the regulated delivery of AMPARs involves GluR4-containing receptors (Zhu *et al*., 2000), and PKA-mediated phosphorylation of this subunit triggers receptor delivery (Esteban *et al*., 2003). Around the second postnatal week, LTP is mostly mediated by the synaptic delivery of GluR2-long (Kolleker *et al*., 2003). Then, later in development, the regulated addition of AMPARs requires both GluR1 phosphorylation by PKA and CaMKII activation (Esteban *et al*., 2003). These developmental changes in the regulation of AMPAR synaptic delivery fit very well with the switch in signalling cascades that are required for LTP induction at different postnatal ages (Yasuda *et al*., 2003).

Local intracellular trafficking of AMPA receptors: role of Rab proteins and the exocyst

It is well established that rapid exocytic events can mediate the delivery of AMPARs into synapses (Luscher *et al*., 1999; Lu *et al*., 2001; Pickard *et al*., 2001; Kopec *et al*., 2006). In this sense, it may come as a surprise that very little is known about the subcellular organization of the membrane trafficking machinery that mediates AMPAR synaptic delivery. This picture has started to change recently, with the identification of local endosomal compartments in close proximity to synapses, or even within dendritic spines, that mediate the delivery of AMPARs into the synaptic membrane (Gerges *et al*., 2004a; Park *et al*., 2004, 2006). These new reports are

starting to offer a glimpse of the complexity of the membrane trafficking machinery operating at postsynaptic terminals, and how it may relate to the subunit-specific synaptic delivery of AMPARs.

Most intracellular membrane sorting in eukaryotic cells is governed by small GTPases of the Rab family (Zerial and McBride, 2001). Therefore, the identification of specific Rab proteins involved in AMPAR trafficking may give us some clues as to how the intracellular sorting and synaptic targeting of AMPARs is organized in neurons. It was recently proposed that recycling endosomes driven by the small GTPase Rab11 mediate the activity-dependent delivery of GluR1-containing AMPARs into synapses (Park *et al*., 2004). In addition, Rab8, which controls *trans*-Golgi network trafficking (Huber *et al*., 1993) and a separate endosomal population (Hattula *et al*., 2006), is also required for GluR1 synaptic insertion and LTP (Gerges *et al*., 2004a). Therefore, it seems that the activity-dependent delivery of AMPARs involves a relay of at least two distinct membrane compartments, whose sorting is controlled by Rab11 and Rab8 possibly acting in separate trafficking steps. Rab11-containing endosomes have recently been localized at the base of dendritic spines (Park *et al*., 2006), whereas ultrastructural studies have detected Rab8 in close proximity to the postsynaptic membrane (Gerges *et al*., 2004a). According to these morphological observations, we propose a model in which AMPARs enter spines through Rab11-dependent endosomes. Subsequently, an additional endosomal population, controlled by Rab8, would drive their insertion into the synaptic membrane (see model in Figure 1).

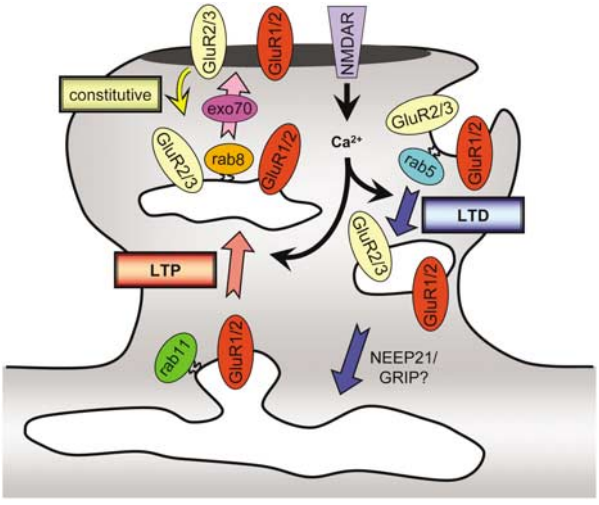

Figure 1 Schematic model for the endosomal membrane trafficking machinery operating at postsynaptic terminals. The activity-dependent entry of GluR1-containing AMPARs into spines is controlled by Rab11 upon LTP induction. Once within the spine, both GluR1–GluR2 and GluR2–GluR3 AMPARs are driven into synapses in an exocytic process controlled by Rab8 and the exocyst subunit Exo70. In addition, GluR2–GluR3 receptors are engaged in constitutive cycling in and out of the postsynaptic membrane. The activity-dependent internalization of AMPARs is mediated by Rab5, acting on the lateral (extrasynaptic) membrane within the spine. Re-entry of internalized receptors into the Rab11–Rab8 delivery circuit may require the participation of NEEP21 and GRIP. AMPARs, AMPA receptors; GRIP1, glutamate receptor-interacting protein 1; LTP, long-term potentiation; NEEP21, neuron-enriched endosomal protein.

As mentioned above, in addition to their activity-dependent synaptic delivery, AMPARs are engaged in constitutive trafficking in and out of synapses. This continuous cycling is thought to involve endocytic and exocytic events (Luscher *et al*., 1999). However, very little is known about the intracellular machinery that controls this process. It has been shown that Rab proteins typically associated with recycling endosomes, such as Rab4 and Rab11, do not participate in constitutive AMPAR synaptic cycling (Gerges *et al*., 2004a). In contrast, Rab8 appears to be critically required (Gerges *et al*., 2004a). Since Rab8 is also involved in activity-dependent trafficking (see above), these results indicate that there is a partial overlap between the endosomal machinery mediating constitutive and regulated delivery of AMPARs at synapses (see model in Figure 1). The endocytic arm of this continuous cycling of receptors is even less characterized. The prototypic Rab protein for endocytosis, Rab5 (Bucci *et al*., 1992), does not participate in constitutive AMPAR internalization (Brown *et al*., 2005). Dynamin was shown to be required for this process (Luscher *et al*., 1999), but the role of clathrin has not been directly tested yet. Obviously, more work will be required to elucidate the cellular basis of this very dynamic aspect of the intracellular trafficking of AMPARs.

The final step in the intracellular trafficking of AMPARs involves their functional insertion and stabilization at the postsynaptic membrane. As mentioned before, several members of the MAGUK family of scaffolding proteins are critical factors for the synaptic targeting of AMPARs (Elias *et al*., 2006). Interestingly, these synaptic scaffolding molecules associate with the exocyst (Riefler *et al*., 2003; Sans *et al*., 2003), a known effector of Rab-dependent exocytic trafficking (Guo *et al*., 1999; Novick *et al*., 2006). Therefore, the exocyst may act as a link between incoming AMPAR-containing vesicles and the synaptic scaffold. In agreement with this scenario, it has recently been shown that the exocyst acts within the dendritic spine to mediate the insertion of AMPARs into the postsynaptic membrane (Gerges *et al*., 2006). In particular, interference with the Exo70 subunit of the exocyst leads to the accumulation of AMPARs within the postsynaptic density, before fusion with the synaptic membrane (Gerges *et al*., 2006). This observation suggests that AMPAR membrane insertion occurs directly at the level of the postsynaptic density (see model in Figure 1).

Activity-dependent internalization and sorting of AMPA receptors

Synaptic AMPARs are internalized in an activity-dependent manner, leading to LTD. This process requires clathrin-mediated endocytosis (Carroll *et al*., 1999; Man *et al*., 2000; Lee *et al*., 2002) (see also review in Carroll *et al*., 2001). Interestingly, and in contrast with constitutive endocytosis, the small GTPase Rab5 drives the regulated internalization of AMPARs during LTD (Brown *et al*., 2005) (see model in Figure 1). In fact, Rab5 is rapidly and transiently activated upon NMDAR activation during LTD induction (Brown *et al*., 2005). Therefore, these results suggest that constitutive and regulated AMPAR internalization may engage different components of the endocytic machinery.

In contrast to the subunit-specific rules for AMPAR delivery, the contribution of different receptor populations to activity-dependent removal still remains controversial. Hippocampal neurons lacking both GluR2 and GluR3 subunits display normal LTD, suggesting that GluR1 removal contributes to synaptic depression (Meng *et al.*, 2003). On the other hand, GluR2 subunits are removed during LTD in hippocampal neurons (Seidenman *et al.*, 2003), and cerebellar LTD requires PKC phosphorylation of GluR2 (Chung *et al.*, 2003). Therefore, both GluR1- and GluR2-containing receptors seem to participate in the synaptic trafficking associated with LTD. In fact, most experimental evidence is compatible with an initial indiscriminate internalization of all AMPAR populations upon LTD induction. However, it is increasingly appreciated that AMPARs undergo complicated intracellular sorting and recycling events after synaptic removal, which may involve significant subunit specificity (Lee *et al.*, 2004).

The molecular mechanisms that organize postendocytic sorting of AMPARs and potential reinsertion into synaptic and/or extrasynaptic membranes are still far from clear. Nevertheless, the balance between GRIP/ABP (AMPAR-binding protein) and PICK1 interactions with GluR2 after PKC phosphorylation seems to be a critical factor (Kim *et al.*, 2001; Perez *et al.*, 2001; Hanley, 2006). In hippocampal and parallel fibre-Purkinje cell synapses, PICK1 appears to drive the synaptic removal of phosphorylated GluR2 receptors (Kim *et al.*, 2001; Chung *et al.*, 2003; Steinberg *et al.*, 2006). This role is facilitated by the calcium-dependent interactions between GluR2 and PICK1 (Hanley and Henley, 2005). Subsequently, a fraction of these internalized GluR2 subunits recycles back into synaptic sites, in a process probably mediated by direct GRIP/ABP–PICK1 interactions (Lu and Ziff, 2005) and NSF-mediated dissociation of the GluR2–PICK1 complex (Hanley *et al.*, 2002). The connection between these AMPAR-binding proteins and the intracellular membrane trafficking machinery is still being elucidated, but it has been recently proposed that the return of AMPARs to synaptic sites may be mediated by phosphorylation-regulated interactions between GRIP/ABP and the endosomal protein NEEP21 (neuron-enriched endosomal protein of 21 kD) (Steiner *et al.*, 2005; Kulangara *et al.*, 2007) (see model in Figure 1).

Conclusions

The field of AMPAR trafficking is advancing at a fast pace. New proteins interacting with AMPARs or with the AMPAR trafficking machinery are constantly being identified. These new investigations are uncovering an intricate choreography, in which AMPARs are assembled, sorted and targeted throughout the neuronal secretory pathway. We are starting to identify the core cellular machinery that transports AMPARs, as well as the regulatory molecules that orchestrate their dynamic behaviour close to the synapse, where bidirectional AMPAR movement results in long-lasting changes in synaptic strength. These are exciting times, when the fields of AMPAR trafficking and synaptic plasticity have begun to be integrated within the realm of cellular biology.

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Conflict of interest

The author states no conflict of interest.

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