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Regulation of AMPA Receptor Trafficking and Synaptic Plasticity

Victor Anggono and **Richard L. Huganir**
Department of Neuroscience, Howard Hughes Medical Institute, The Johns Hopkins, University School of Medicine, Baltimore, Maryland 21205

Abstract

AMPA receptors (AMPARs) mediate the majority of fast excitatory synaptic transmission in the brain. Dynamic changes in neuronal synaptic efficacy, termed synaptic plasticity, are thought to underlie information coding and storage in learning and memory. One major mechanism that regulates synaptic strength involves the tightly regulated trafficking of AMPARs into and out of synapses. The life cycle of AMPARs from their biosynthesis, membrane trafficking and synaptic targeting to their degradation are controlled by a series of orchestrated interactions with numerous intracellular regulatory proteins. Here we review recent progress made towards the understanding the regulation of AMPAR trafficking, focusing on the roles of several key intracellular AMPAR interacting proteins.

Introduction

The mammalian central nervous system is comprised of the incredibly complex connectivity between billions of neurons that are highly specialized for the fast processing and transmission of cellular signals. Communication between neurons, each of which contains thousands of synapses, underlies all basic and higher-order information processing essential for normal brain function. The ability of neural circuits to strengthen or weaken their connectivity forms a molecular basis underlying the experience-dependent changes in adaptive behaviors.

Synaptic plasticity can be regulated at the presynaptic side by altering the efficacy of neurotransmitter release, or on the postsynaptic side by changing the density, types and properties of neurotransmitter receptors. AMPA receptors (AMPARs) are the principal ionotropic glutamate receptors that mediate fast excitatory synaptic transmission in mammalian brain. AMPARs are tetrameric assemblies of highly homologous subunits encoded by four different genes, GluA1-4. The trafficking of AMPARs into and out of synapses is highly dynamic and is regulated by subunit specific AMPAR-interacting proteins as well as by various post-translational modifications that occur on their cytoplasmic carboxyl terminal (C-terminal) domains. The regulated trafficking of AMPARs is a major mechanism underlying activity-induced changes in synaptic transmission. In general, increases in AMPAR function at synapses result in the long-term potentiation (LTP) of synaptic strength, whereas removal of synaptic AMPARs leads to long-term depression

*Corresponding author: Dr. Richard L. Huganir, Department of Neuroscience, Howard Hughes Medical Institute, The Johns Hopkins University School of Medicine, 725 North Wolfe Street, Hunterian 1009A, Baltimore, MD 21205, rhuganir@jhmi.edu, Phone: +1-410-955-4050, Fax: +1-410-955-0877.

(LTD) [1]. This review focuses on recent advances providing new insights into the molecular control of AMPAR trafficking by proteins that directly interact with the intracellular domains of GluA1 and GluA2.

AMPAR Structure and Subunit Composition

All AMPAR subunits consist of highly homologous extracellular and transmembrane regions, but vary in their intracellular C-terminal domains. The GluA1, GluA4 and an alternatively spliced form of GluA2 (GluA2L) contains long C-terminal domains, whereas the GluA2, GluA3 and an alternatively spliced form of GluA4 (GluA4S) have shorter C-terminal domains (Figure 1). Expression of these subunits is developmentally regulated and is region specific. The C-termini of AMPAR subunits contains multiple regulatory elements that are subjected to various post-translational modifications, including protein phosphorylation, palmitoylation and ubiquitination. They also interact with scaffold proteins that bind signaling molecules as well as cytoskeletal proteins. Hence, the C-terminal domains of these subunits are crucial for the regulation of AMPAR function, including channel gating, trafficking and stabilization at synapses [1,2].

AMPARs are assembled as two identical heterodimers with GluA1/2 being the most predominant AMPAR subtype in hippocampal pyramidal neurons, followed by GluA2/3 heteromers [3]. The presence of GluA2 subunit has a profound impact on the biophysical property of AMPAR heteromeric complexes such that the GluA2-containing AMPARs are Ca^{2+}-impermeable with linear current-voltage relationship while GluA2-lacking receptors are Ca^{2+}-permeable and have an inwardly rectifying current-voltage relationship. The subunit composition of AMPARs also governs the rules of AMPAR trafficking. The long-tailed AMPARs are important for the activity-dependent insertion of AMPARs to synapses during synaptic strengthening, such as LTP, whereas the short-tailed AMPARs appear to constitutively recycle in and out of synapses in the absence of activity, while internalization of both forms of AMPARs occurs during activity-dependent synaptic weakening, such as LTD [4].

AMPA Receptor Trafficking

The number of AMPARs at synapses is dependent on relative rates of exocytosis and endocytosis at the postsynaptic membrane. Enhanced receptor exocytosis and recycling occur during synaptic potentiation, while increased rate of endocytosis results in LTD [1,4]. The delivery of AMPARs to the synapse requires dynein- or kinesin-dependent transport of AMPARs-containing vesicles (or endosomes) and SNARE-mediated fusion events at the plasma membrane. Recent studies have identified myosinVa and Vb as the Ca^{2+}-sensitive motor proteins that deliver cargo vesicles containing AMPARs [5,6], as well as SNAP-23 and syntaxin-4 as the postsynaptic v- and t-SNAREs, respectively [7,8]. AMPARs are inserted into the plasma membrane in the soma or dendrites at extrasynaptic sites and travel to dendritic spines via lateral diffusion [9-11]. However, the exact site of AMPAR exocytosis during LTP remains an ongoing debate. Several studies have reported that AMPARs first appear exclusively in the dendrites and are subsequently incorporated into synapses [12,13], while some have shown direct insertion of AMPARs both into spines and dendrites [6,8,14].

On the other hand, clathrin- and dynamin-mediated endocytosis of AMPARs mainly occurs at the somatodendritic plasma membrane as well as at endocytic zone (EZ) adjacent to the postsynaptic density (PSD) following NMDA treatment [15,16]. Depending on the type of stimulation, internalized AMPARs undergo complex endosomal sorting processes that direct receptors either to recycle back to the plasma membrane or to be degraded by the lysosomal

pathway [17,18]. Local endocytosis and recycling at EZ may provide a pool of mobile AMPARs to maintain synaptic strength during LTP [19,20].

AMPA Receptor Interacting Proteins

As mentioned above, subunit composition of AMPARs determine the routes of AMPAR trafficking, such that GluA1 is dominant over GluA2 during activity-dependent AMPAR exocytosis, while GluA2 is the primary determinant during endocytosis and post-endocytic endosomal sorting [1]. This differential regulation is mainly due to interactions of intracellular C-terminal domain of GluA subunits with various components of the PSD and their associated proteins that function during receptor internalization and exocytosis.

Synaptic Associated Protein 97 kDa (SAP97)

SAP97 belongs to the PSD95-like membrane-associated guanylate kinase (PSD-MAGUK) protein family, which include PSD93, PSD95 and SAP102. Despite being the first protein shown to bind directly to GluA1 C-terminal domain, the exact function of SAP97 has remained elusive [21]. SAP97 also interacts with PKA anchoring molecule AKAP79 [22], which may enhance GluA1 phosphorylation at Ser-845 that can regulate LTP [23]. However, SAP97 has also been shown to act early in the secretory pathway to facilitate maturation of AMPARs [24]. While some studies have shown that overexpression of SAP97 increases AMPAR function at synapses [25,26], some have suggested otherwise [27,28]. Nonetheless, expression of SAP97 is able to rescue AMPAR transmission reduced by loss of PSD95 and PSD93 function, suggesting a functional redundancy among PSD-MAGUK members [27,29].

It has long been postulated that LTP activates CaMKII, which in turn phosphorylates GluA1 and other proteins that may interact with PDZ motif of GluA1 [1]. SAP97 is believed to play critical role in AMPAR trafficking and LTP since it interacts with the PDZ motif of GluA1 and is targeted into spines upon CaMKII phosphorylation [30]. However, knock-in mice lacking GluA1 PDZ motif show normal GluA1 synaptic localization and hippocampal LTP [31]. This result is further corroborated by a recent study showing that SAP97 conditional knockout mice have normal LTP [29]. Further study is required to determine the precise function of SAP97 in AMPAR trafficking and synaptic plasticity.

Protein 4.1N

The actin cytoskeleton immobilizes glutamate receptors at synapses and plays a crucial role in basal synaptic transmission and synaptic plasticity [32]. Protein 4.1N contains a spectrin/actin-binding domain and binds directly to the membrane proximal region of GluA1 C-terminal domain and regulate surface expression of GluA1 [33]. GluA1 and 4.1N interaction is enhanced by PKC phosphorylation of GluA1 on Ser-816 and Ser-818 but is negatively regulated by GluA1 palmitoylation on Cys-811 [10,34]. A recent study showed that acute knockdown of protein 4.1N decreases the frequency of GluA1 plasma membrane insertion on extrasynaptic sites and impairs the maintenance phase of LTP [10]. Although another study showed normal basal synaptic transmission and LTP in 4.1N/4.1G double knockout mice [35], recent results have shown that LTP maintenance is impaired in the 4.1N/4.1G/4.1B triple knockout mice (Nils Brose, personal communication) indicating significant functional redundancy in this family of proteins.

Glutamate Receptor Interacting Protein (GRIP)

GRIP1 and GRIP2 (also called AMPAR binding protein/ABP) are two homologous proteins that contain seven PDZ domains and interact directly with GluA2/3 C-terminal domains through their fourth and fifth PDZ domains [36,37]. The interaction of GRIP1 and 2 with

GluA2/3 regulates the membrane trafficking and synaptic targeting of AMPARs and is critical for several forms of synaptic plasticity. Interestingly, the binding of GluA2 to GRIP1 is disrupted upon GluA2 phosphorylation on Ser-880 and Tyr-876 [38,39]. Since GluA2 Ser-880 phosphorylation is crucial for the expression of LTD in both hippocampal SC-CA1 and cerebellar parallel fiber-Purkinje cell synapses, it has been hypothesized that detachment of GRIP1 upon Ser-880 phosphorylation increases the internalization rate of AMPARs leading to LTD [40-42]. Importantly, cerebellar LTD is completely absent in the GRIP1/2 double knockout mice [43].

Although GRIP1 and 2 are important for plasticity, how GRIP1/2 regulates AMPAR trafficking is an active area of investigation. Early studies suggested that GRIP1 interaction with kinesin heavy chain [44] and liprin-α, which binds to another kinesin-family member, KIF1A [45,46], is important for AMPAR delivery to dendrites and synaptic targeting. Some studies, however, suggested that GRIP1 might function to retain AMPARs intracellularly [47,48]. Recently, several studies have reported a role for GRIP1 in regulating AMPAR endosomal recycling. GRIP1 binding to neuron-enriched endosomal protein 21kDa (NEEP21) promotes recycling of internalized AMPARs back to the plasma membrane through the recycling pathway [49,50]. Disruption of GRIP1 and NEEP21 interaction induces aberrant accumulation of AMPARs in early endosomes and lysosomes, reduces GluA2 surface expression, which in turns abolishes the maintenance of LTP [49,51]. Live-cell imaging analyses also reveal a delayed rate of AMPAR recycling following NMDA-induced endocytosis when measured using a GluA2 mutant that can not interact with GRIP1 [52]. More importantly, AMPAR recycling is also slower in GRIP1/2 double knockout neurons [53]. The interaction between GRIP1 and Sec8, a core component of the exocyst complex, which has been implicated in AMPAR targeting and insertion to the plasma membrane, could explain the recycling rate deficit seen in GRIP1/2 knockout neurons [53,54].

GRIP1 also directly interacts with GRIP-associated protein 1 (GRASP-1), a neuron-specific effector of Rab4 that regulates the directionality of AMPAR endosomal trafficking [55,56]. GRASP-1 facilitates the segregation of Rab4 from early endosomes and coordinates the coupling to recycling endosomes by interacting with the endosomal SNARE syntaxin 13 [56]. Knockdown of GRASP-1 reduces activity-dependent recycling of AMPARs and maintenance of late phase LTP in hippocampal slices [56]. Whether or not GRIP1 is required for GRASP-1-mediated endosomal coupling still remains an open question. In addition, a newly identified AAA-ATPase, Thorase, directly interacts with GRIP1 and promotes the disassembly of GRIP1-AMPAR complexes in an activity-dependent manner [57]. Genetic deletion of Thorase results in the reduction in AMPAR internalization, impaired LTD as well as deficits in learning and memory [57].

Recently, a genetic study has identified a number of rare missense mutations within *GRIP1* gene encoding PDZ4-6 in patients with autism [58]. They are gain-of-function *GRIP1* variants as they accelerate the rate of AMPAR recycling and increase surface expression of GluA2 in neurons [58]. Genetic ablation of GRIP1/2 abolished the expression of cerebellar LTD [43], but more importantly these mice exhibit increased sociability and impaired prepulse inhibition [58]. Together, these studies suggest critical roles of GRIP1/2 in controlling AMPAR trafficking, synaptic plasticity and social behavior.

Protein Interacting with C-kinase 1 (PICK1)

PICK1 is a BAR domain containing protein that directly interacts with GluA2/3 C-terminal domains through its PDZ domain [59]. It is well established that PICK1-GluA2 interaction is required for both hippocampal and cerebellar LTD [40,60-63]. This has led to a model whereby PICK1 drives synaptic removal of GluA2-containing AMPARs [64]. Elevated

levels of intracellular [Ca^{2+}] and increased PKC activity upon LTD induction result in dissociation of GRIP1 and *N*-ethylmaleimide-sensitive factor (NSF) from GluA2 and enhanced PICK1 binding to GluA2 and a vesicle fusion protein, β-SNAP to promote internalization of AMPARs [65-67]. The binding of GluA2 is thought to induce a conformational change in PICK1 into an "open" confirmation that enhances its interaction with Arp2/3 complex and actin filaments [68]. This interaction may inhibit actin polymerization, reducing tension on the plasma membrane allowing membrane bending during clathrin-coated pit formation, potentially by the BAR domain of PICK1 itself.

Recent studies, however, have suggested an alternative function for PICK1 in retaining the internalized AMPARs intracellularly [52,63,69,70]. PICK1 knockdown has been shown to accelerate the rate of GluA2 recycling following NMDA stimulation and reduce intracellular AMPAR accumulation [69,70]. The rate of AMPAR recycling is also increased in the PICK1 knockout mice [52]. In line with these observations, PICK1 has been found to localize in the early and recycling endosomes, and its colocalization with early endosomal marker Rab5 is rapidly enhanced following NMDA stimulation [71,72]. Since the activity Arp2/3 complex is required for the maturation and fission of endosomes, the recruitment of PICK1 to the early endosomes could delay this process and prolong the retention of intracellular AMPARs [73,74].

PICK1 has recently been shown to interact with KIBRA, a protein encoded by a memory-associated gene in human [75]. Loss of KIBRA function phenocopies many defects in AMPAR trafficking, synaptic plasticity and behavioral phenotypes seen in PICK1 knockout animals [75], suggesting that KIBRA and PICK1 act within the same pathway to regulate AMPAR trafficking. Interestingly, PICK1 and KIBRA, similar to GRIP1, also interact with Sec8, a member of the exocyst complex. This suggests that the PICK1-KIBRA-Sec8 complex may interfere with the delivery of vesicles containing AMPARs from the recycling endosomes to the plasma membrane. However, the precise molecular role of PICK1 in regulating AMPAR endosomal trafficking is not clear.

PICK1 also plays a differential role in regulating the membrane trafficking of GluA2-containing and GluA2-lacking Ca^{2+}-permeable AMPARs (CP-AMPARs). Overexpression of PICK1 reduces surface expression of GluA2 and facilitates the expression of CP-AMPARs in cultured neurons [76]. Conversely, surface expression of CP-AMPARs is decreased in PICK1 knockout neurons, while the levels of surface GluA2/3 receptors are elevated [69,77]. Interestingly, specific forms of synaptic plasticity that dynamically regulate the differential expression of CP-AMPARs at synapses are abolished in PICK1 knockout animals [77-79]. The exact mechanism on how PICK1 regulates the expression of CP-AMPARs is unclear. Presumably, PICK1 might selectively retain the intracellular pool of GluA2 during AMPAR endosomal trafficking hence regulating dynamic changes in CP-AMPARs synaptic targeting. PICK1 may also delay the maturation of GluA2-containing receptors in the ER and Golgi during biosynthesis of AMPAR [69,80].

Transient incorporation of synaptic CP-AMPARs has been observed at an early stage of hippocampal LTP induction and loss of PICK1 function has been reported to prevent the expression hippocampal LTP [62,81]. However, the recruitment of CP-AMPARs during LTP is controversial [82,83] and the role of PICK1 in LTP appears to be complex [61,70]. A systematic study in PICK1 knockout mice has revealed a selective requirement of PICK1 in hippocampal LTP in an induction protocol- and an age-dependent manner [61]. Loss of PICK1 has no significant effect on synaptic plasticity in juvenile mice but impairs some forms of LTP in adult mice. In support of this observation, hippocampal-dependent inhibitory avoidance learning is impaired only in adult knockout mice.

N-ethylmaleimide-sensitive factor (NSF)

NSF, an essential component of SNARE-mediated fusion machinery, directly binds to the carboxyl-terminus juxtamembrane region of GluA2 [84-86]. This interaction is required for direct insertion of GluA2 into the plasma membrane, as well as its rapid incorporation and stabilization at synapses [87,88]. In agreement with these observations, disruption of GluA2-NSF interaction causes a run-down in AMPAR-mediated synaptic currents [84,85,89,90]. Likewise, the binding of polo-like kinase-2 to NSF is sufficient to disrupt GluA2-NSF interaction and induce removal of surface GluA2 [91]. Moreover, infusion of peptides that disrupt GluA2-NSF interaction inhibits PKMζ-induced synaptic potentiation [92] and formation of fear memory in lateral amygdala [93].

NSF appears to participate in AMPAR endosomal forward trafficking, in part by regulating the interaction between GluA2 and PICK1 in a Ca^{2+}-dependent manner [66,67]. Under basal low [Ca^{2+}] condition, NSF interaction with GluA2 may reduce intracellular retention of GluA2 by PICK1, and hence maintain constitutive recycling of GluA2 and stabilize AMPARs at synaptic sites. GluA2 mutant devoid of NSF binding exhibits a greatly reduced recycling rate upon NMDA stimulation and is mis-sorted into NEEP21-negative endosomes and late endosomes [18,52,87]. On the other hand, elevated [Ca^{2+}] during LTD decreases NSF-GluA2 interaction, which in turns promotes GluA2-PICK1 interaction and prolongs intracellular retention of internalized GluA2 in endosomal compartments. Conversely, enhancement of GluA2-NSF interaction through *S*-nitrosylation of NSF in response to glycine stimulation increases surface expression of GluA2 [94].

AP-2 and BRAG-2

AMPAR internalization is mediated by dynamin-dependent clathrin-mediated endocytosis [1]. The μ2-subunit of AP-2 adaptor directly interacts with GluA2 C-terminus that overlaps with NSF binding site [89,95]. This interaction is involved specifically in NMDA-induced internalization of AMPARs and NMDA-dependent hippocampal LTD [89]. Recently, BRAG2, which functions as a guanine-exchange factor for the coat-recruitment GTPase Arf6, has been also been shown to interact with GluA2 C-terminal domain [96]. This interaction is regulated by GluA2 phosphorylation on Tyr-876, and is important for mGluR-induced internalization of AMPARs and mGluR-dependent LTD [96]. Interestingly, activation of Arf6 triggers local increase in phosphatidyl-inositol (4,5)-bisphosphate, which mediates the recruitment of AP-2 and formation of clathrin-coated vesicles at the plasma membrane [97]. However, the cooperative action of BRAG2 and AP-2 in mediating AMPARs internalization and LTD is yet to be determined.

Concluding Remarks

Cumulative evidence over the past two decades has placed AMPAR trafficking as a major regulatory mechanism in controlling synaptic plasticity, learning and memory. The past few years have seen a rapid progress in the field revealing the complexity of AMPAR trafficking pathways (Figure 2). More importantly, the molecular details regulating AMPAR endosomal trafficking and sorting have started to be elucidated through identification of new AMPAR interacting proteins and study of genetically modified mice. Future studies concerning the cross talk between various signaling pathways, intermolecular regulation between AMPAR interacting proteins, and identification of molecular cues that determine the sorting of AMPARs into distinct intracellular compartments under basal, stimulated and pathological conditions are crucial to better understand mechanisms of AMPAR trafficking and ultimately its role in higher brain function.

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Highlights

- Highly dynamic trafficking of AMPARs regulates synaptic strength and plasticity.
- Subunit-specific AMPAR interacting proteins regulate receptor trafficking.
- Genetic deletion of AMPAR interacting proteins impairs synaptic plasticity, learning and memory.

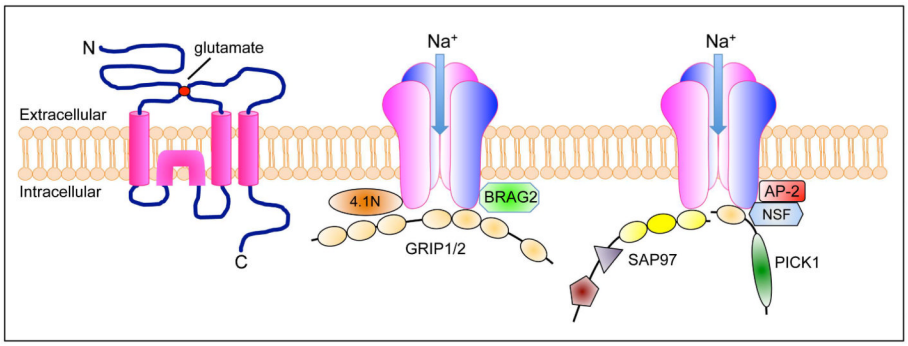

Figure 1.

Structure of AMPAR and its direct interacting proteins. AMPAR is a tetrameric channel assembled from two dimers of different subunits, such as GluA1/GluA2 and GluA2/GluA3. Each individual subunit is composed of a large extracellular ligand-binding domain and a short intracellular carboxyl-tail linked by four transmembrane domains. GluA1 C-terminal domain contains type I PDZ ligand and directly interacts with SAP97, whereas GluA2 C-terminal domain contains type II PDZ ligand and interacts directly with PICK1 and GRIP1. In addition, GluA1 also interacts with protein 4.1N through its juxtamembrane region of the C-terminus, while GluA2 interacts with AP-2, NSF and BRAG-2 through it C-terminus in a non PDZ-dependent manner. Direct binding of AMPARs and these interacting proteins regulates various steps in AMPAR trafficking.

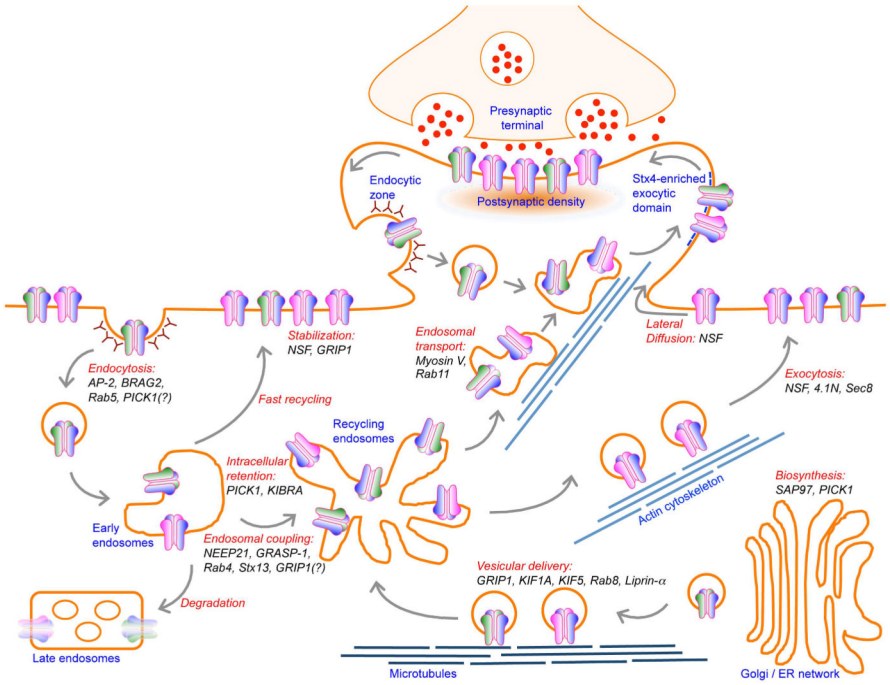

Figure 2.

Routes of AMPAR trafficking. AMPARs are assembled in the endoplasmic reticulum and Golgi apparatus in the soma and are delivered into the dendrite via kinesin-dependent vesicular trafficking on microtubule networks prior to their insertion to the plasma membrane. Via lateral diffusion, surface AMPARs are incorporated into synapse and stabilized by postsynaptic density scaffolding proteins. Mature AMPARs undergo constitutive recycling through endosomal trafficking pathway. AMPARs are internalized from the plasma membrane by clathrin-mediated endocytosis and traffic to the early endosome. From early endosome, AMPARs can be delivered back to the plasma membrane either directly (fast recycling) or through recycling endosome, or entering the degradation pathway through late endosome. During LTD, the rate of AMPAR internalization outweighs the rate of AMPAR exocytosis, resulting in reduced number of synaptic AMPARs. Depending on the LTD stimulus, internalized AMPARs can either be retained in intracellular compartment or be degraded in lysosome. Conversely, during LTP, AMPARs are constantly delivered to the plasma membrane to induce early burst and long-term maintenance of synaptic potentiation. Under certain LTP stimuli, recycling endosomes containing AMPARs are directly inserted into dendritic spine exocytic domain, marked by the presence of t-SNARE syntaxin-4. The dendritic spine microdomain also includes a specialized endocytic zone, where AMPARs are rapidly internalized and recycled to provide a large pool of AMPARs during LTP. These highly complex pathways of AMPAR trafficking are tightly regulated by a series of orchestrated interactions with key intracellular regulatory molecules. Disruption of AMPAR binding to its interacting proteins shown in this diagram often leads to aberrant AMPAR trafficking, impaired synaptic plasticity and deficits in learning and memory.