The Cell Biology of Synaptic Plasticity: AMPA Receptor Trafficking

Jason D. Shepherd[1] and Richard L. Huganir[2]

[1]The Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139; email: jshephe@mit.edu

[2]Department of Neuroscience, Howard Hughes Medical Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205; email: rhuganir@jhmi.edu

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Abstract

The cellular processes that govern neuronal function are highly complex, with many basic cell biological pathways uniquely adapted to perform the elaborate information processing achieved by the brain. This is particularly evident in the trafficking and regulation of membrane proteins to and from synapses, which can be a long distance away from the cell body and number in the thousands. The regulation of neurotransmitter receptors, such as the AMPA-type glutamate receptors (AMPARs), the major excitatory neurotransmitter receptors in the brain, is a crucial mechanism for the modulation of synaptic transmission. The levels of AMPARs at synapses are very dynamic, and it is these plastic changes in synaptic function that are thought to underlie information storage in the brain. Thus, understanding the cellular machinery that controls AMPAR trafficking will be critical for understanding the cellular basis of behavior as well as many neurological diseases. Here we describe the life cycle of AMPARs, from their biogenesis, through their journey to the synapse, and ultimately through their demise, and discuss how the modulation of this process is essential for brain function.

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INTRODUCTION

AMPAR: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

All brain processes, such as the ability to learn and remember and those involved in our emotions and intelligence, consciousness, and all human behavior, are possible because of the incredibly complex connectivity between neurons in the brain. Moreover, the ability to process information and learn in response to experience is due to continual changes in neuronal communication. Thus, it is not surprising that the molecular and cellular mechanisms that regulate neuronal connectivity are highly complex and exquisitely regulated. In many ways the cellular processes found in neurons are unique; neurons have adapted and evolved common cell biological pathways to fit their needs. This is particularly evident in the processes that regulate synaptic function. Single neurons have thousands of synapses that can act as their own autonomous computational units. Synaptic transmission at individual synapses is regulated mostly by changes in neurotransmitter release or in neurotransmitter receptor function. Glutamate receptors mediate most excitatory neurotransmission and have been intensively investigated. The study of the AMPA-type glutamate receptors (AMPARs), in particular, has proved useful in elucidating many of the cell biological processes involved in synaptic function. AMPARs are ligand-gated ion channels and are the main mediators of excitatory neurotransmission in the brain. Other glutamate receptors such as the NMDA and metabotropic receptors (mGluRs) also play important roles in neuronal function. NMDA receptors (NMDARs) are voltage- and ligand-gated channels that are calcium permeable and are important regulators of synaptic plasticity. mGluRs are G protein–coupled receptors that act through diverse signaling pathways to modulate neurotransmission. However, it is arguably the AMPARs that have provided the most insight into the role of membrane trafficking mechanisms in synaptic plasticity.

Here we review recent progress in the regulation of AMPAR trafficking. We highlight how neurons have adapted common cell biological processes to regulate AMPARs, which ultimately has important implications for brain function.

AMPA RECEPTOR BIOGENESIS

Structure and Composition

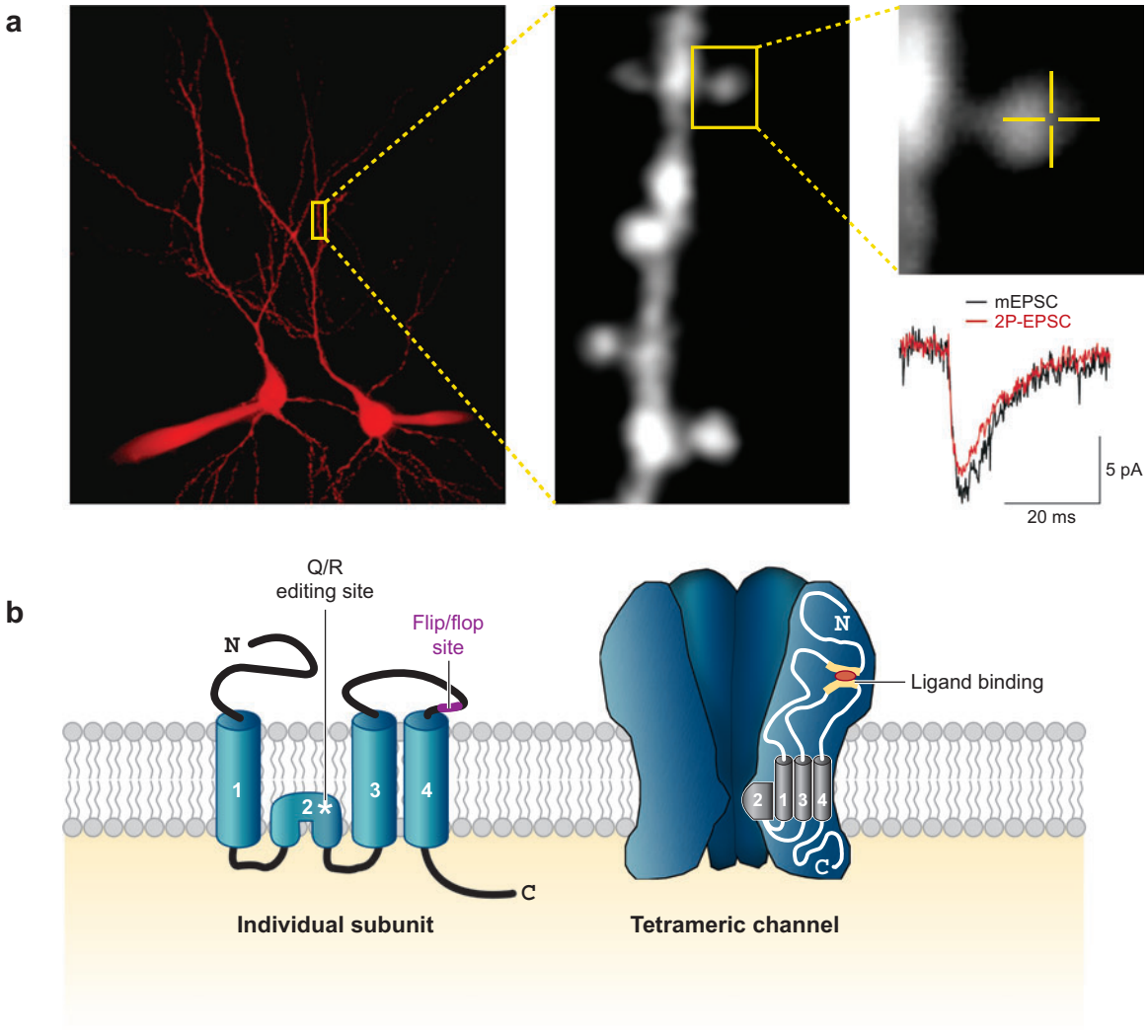
The AMPARs consist of four closely related genes that encode the four subunits GluR1–4 or A–D (**Figure 1**). These subunits combine in different stoichiometries to form ion channels with distinct functional properties (Hollmann & Heinemann 1994). The

extracellular and transmembrane regions of AMPAR subunits are very similar but vary in their intracellular cytoplasmic tails. The GluR1 and -4 and an alternative splice form of GluR2 (GluR2L) have long cytoplasmic tails. In contrast, the predominant splice form of GluR2 has a short tail similar to GluR3 and an alternative splice form of GluR4 (GluR4S). Expression of the receptor subunits is developmentally regulated and is brain region specific. Alternative splicing of the C-terminal domains determines the binding of the subunits to specific interacting proteins as well as the modes of regulation of the receptors by protein phosphorylation (see below; Song & Huganir 2002). All four AMPAR subunits also occur in two alternatively spliced versions, flip and flop, that are encoded by exons 14 and 15 (Sommer et al. 1990), and form part of the extracellular ligand-binding domain (LBD). This splicing event is regulated both developmentally and regionally and influences the pharmacologic and kinetic properties of the channel (Monyer et al. 1991). The flop versions generally desensitize much more rapidly than the flip forms in response to glutamate (Sommer et al. 1990). Furthermore, the flop channels are less responsive to the pharmacological agent cyclothiazide, which blocks desensitization. AMPARs are also regulated by RNA editing, a process involving enzymatic deamination of ribonucleotides in prespliced mRNA (Bass 2002). Editing of a glutamine codon to an arginine codon (Q/R editing) in the ion channel pore region of the GluR2 subunit regulates the calcium permeability and channel rectification of the ion channel as well as endoplasmic reticulum (ER) retention of the subunit (see below). Arginine-to-glycine (R/G) editing in the S2 loop of GluR2–4 alters resensitization kinetics; edited G forms recover from desensitization quicker (Lomeli et al. 1994). Not much is known about the regulation of these splicing and editing events. Alternative splicing in neurons is regulated by neuronal activity, such as the splicing of the NR1 subunit of the NMDAR (Mu et al. 2003); however, it is unclear whether activity regulates splicing or editing of AMPAR subunits.

ER: endoplasmic reticulum

Transcriptional and Translational Regulation

Many neurotransmitter receptors are found only in neurons and in some cases are restricted to certain subpopulations of neurons. AMPAR subunit mRNAs are found almost exclusively in neurons and certain glia, including Bergmann glia in the cerebellum and oligodendrocyte precursor cells throughout the brain (Bergles et al. 2000). This transcriptional specificity has been studied in the GluR1 and GluR2 genes and maps to the promoter regions. The GluR2 promoter contains the regulatory element for the RE1-silencing transcription factor (REST) that silences GluR2 expression in nonneuronal cells (Borges & Dingledine 2001, Myers et al. 1998). The regulation of transcription and translation is an obvious mechanism for the control of protein expression, but in neurons transcription and translational processes are extremely dynamic and have evolved into highly elaborate and crucial regulatory mechanisms of neuronal function (Sutton & Schuman 2006). In particular, neurons have evolved specific pathways to transport mRNA out into dendrites, where subsequent local translation can occur (**Figure 2**). All the requisite machinery for translation, such as ribosomes and elongation and initiation factors, is found in dendrites. Most of the mRNAs transported to dendrites are those of synaptic proteins involved in modulating synaptic transmission, including the immediate early gene (IEG) *Arc*, calcium/calmodulin-dependent protein kinase II (CaMKII), and the growth factor brain-derived neural factor (BDNF). In addition, some of the AMPAR subunit mRNAs are dendritically localized, suggesting that local synthesis of AMPAR subunits regulates local receptor abundance and composition (Grooms et al. 2006, Ju et al. 2004, Kacharmina et al. 2000). Using the arsenic-based dyes FlAsH and ReAsH, Malenka and



colleagues showed that transfected tagged GluR1 and 2 subunits can be synthesized in specific dendritic compartments that are independent of the soma (Ju et al. 2004). In addition, a recent study has shown that the endogenous mRNAs for GluR1 and -2 are localized to proximal and distal dendrites of hippocampal neurons. A number of GluR2 mRNA clusters were localized at synaptic sites, and glutamatergic signaling regulated the abundance as well as the localization of GluR1 and -2 mRNAs (Grooms et al. 2006). Intriguingly, NMDAR activation resulted in a decrease in mRNA abundance, which was dependent on a rise in intracellular calcium and activation of the ERK (extracellular signal–regulated kinase)/MAPK(mitogen-activated protein kinase) signaling pathway, ultimately leading to transcriptional arrest. In contrast, group I mGluR activation increased dendritic AMPAR mRNA by an increase in microtubule-dependent anterograde mRNA transport. Precisely how and to what degree local synthesis of AMPARs contributes to synaptic function and plasticity remain to be determined. Activation of both NMDARs and mGluRs can induce long-lasting forms of plasticity (see below) through distinct complex mechanisms and pathways. Dopamine receptors also regulate local synthesis of AMPARs. Local application of a dopamine D1/D5 receptor agonist to dendrites led to a rapid, protein-synthesis-dependent increase in the frequency of spontaneous miniature excitatory postsynaptic currents (mEPSCs) (Smith et al. 2005). In addition, D1/D5 leads to an increase in endogenous protein synthesis, with GluR1 as one of the proteins upregulated, suggesting that GluR1 synthesis may underlie the changes in mEPSC frequency. How dopamine receptors regulate protein synthesis remains to be established.

EPSC: excitatory postsynaptic current

GRIP: glutamate receptor–interacting protein

NSF: *N*-ethylmaleimide-sensitive fusion protein

PICK1: protein interacting with C kinase 1

Biosynthesis in the Endoplasmic Reticulum

The basic machinery for the production of transmembrane proteins is highly conserved in eukaryotic cells, and neurons are no exception. However, owing to the unique structure and function of neurons, the secretory process is highly elaborate (Kennedy & Ehlers 2006). The four AMPAR subunits, GluR1–4, assemble in different combinations to form tetrameric channels (Rosenmund et al. 1998). Most AMPARs are composed of GluR1-GluR2 or GluR2-GluR3 combinations, although the numbers and percentage of combinations vary in different brain regions and during development. Similar to most other

Figure 1

Structure and composition of AMPA receptors (AMPARs). (*a*) Activation of AMPARs by two-photon (2P) uncaging of MNI-glutamate. Whole-cell recordings were obtained from two pyramidal neurons of the CA1 region of the hippocampus. Alexa 594 (10 μM) was included in the recording solution to outline neuronal morphology. A 2P image of a dendritic region is shown; dendritic spines can readily be observed. A spine is further magnified to show where MNI-glutamate was uncaged to activate AMPARs (0.5 μM; *orange lines* define the region of uncaging, which is at the *center* of the *cross*). Traces of averaged miniature excitatory postsynaptic currents (mEPSCs) and AMPAR-mediated currents elicited by 2P uncaging recorded from the same neuron are superimposed. Note the comparable kinetics of the two currents (provided by Jean-Claude Béïque). (*b*) Structure of the AMPAR subunits and the tetrameric channel. The individual subunits are composed of four transmembrane domains, and the channel consists of four subunits, which are usually two dimers. The dimers are usually two different subunits, such as GluR1 and -2 or GluR2 and -3. (*c*) AMPAR C termini differ in their amino acid sequence, which determines their interacting partners. Various phosphorylation sites and binding partners are highlighted. Protein abbreviations: AP-2, adaptor protein-2; CaMKII, calcium/calmodulin-dependent protein kinase II; GRIP, glutamate receptor–interacting protein; NSF, *N*-ethylmaleimide-sensitive fusion protein; PICK1, protein interacting with C kinase 1; PKA, protein kinase A; PKC, protein kinase C; SAP97, synapse-associated protein 97.

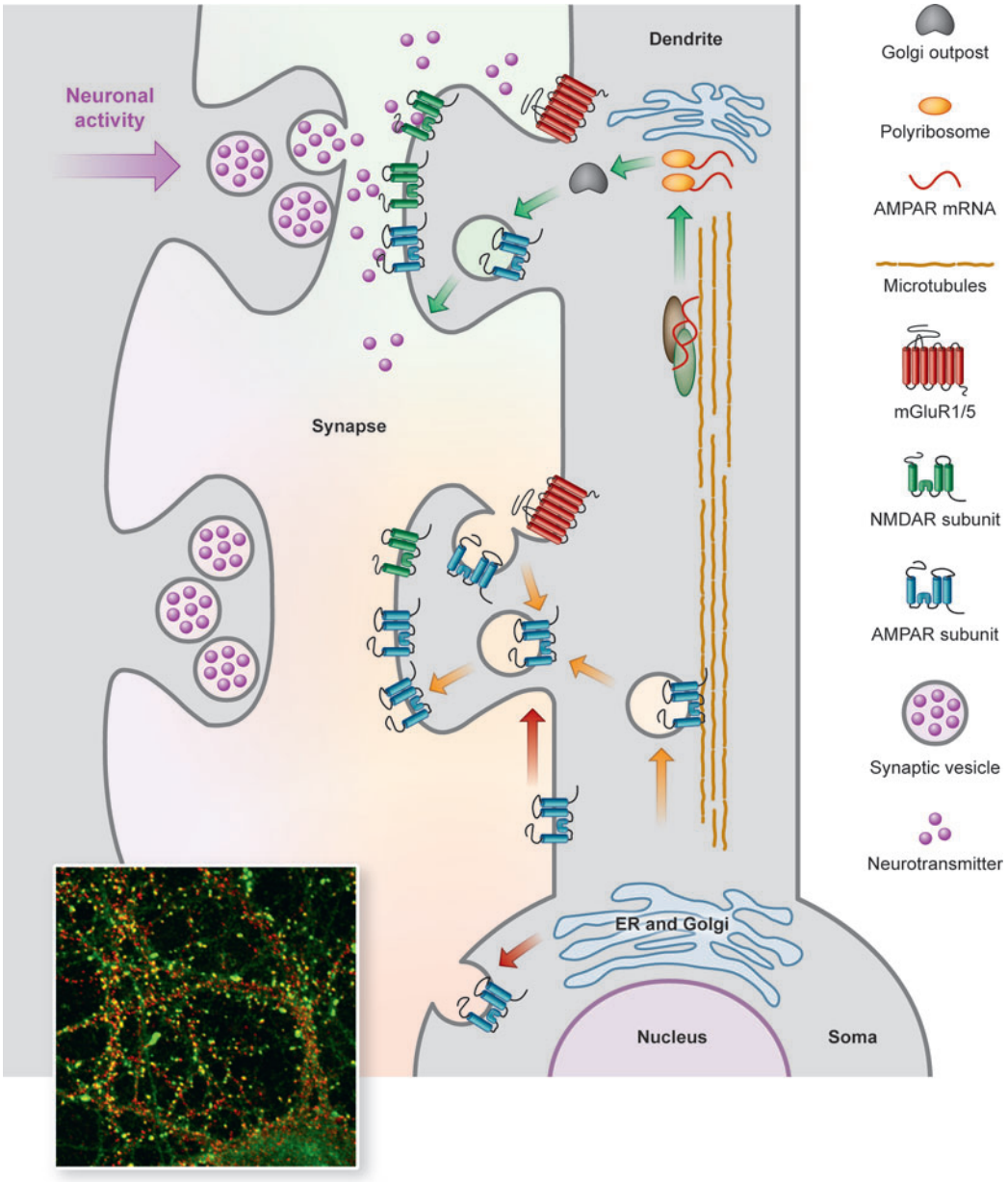


Figure 2

AMPA receptor (AMPAR) trafficking. AMPARs are synthesized in the endoplasmic reticulum (ER) and Golgi in the cell body and are inserted into the plasma membrane either at the soma (*dark red arrows*) or at synapses (*yellow arrows*). Receptors inserted in the soma may travel to synaptic sites via lateral diffusion. Receptors may be inserted or removed locally at synaptic sites (see **Figure 3**). Receptors can also be synthesized locally in dendrites (*green arrows*). Subunit mRNA is trafficked out into dendrites via a RNA-protein complex traveling along the cytoskeleton. mRNA can be translated by local polyribosomes in response to neuronal activity mainly through metabotropic receptor 1 and 5 (mGluR1/5) activation. Membrane proteins can be processed in dendrites via Golgi outposts. The inset at lower left shows a cultured hippocampal neuron stained for PSD-95 (*green*), a postsynaptic marker, and surface GluR1 (*red*).

multimeric membrane proteins, AMPARs are first assembled in the ER. Once in the ER, the N-terminal signal sequence is cleaved, and a high-mannose glycosylation attaches to the first extracellular domain at specific asparagine residues (Rogers et al. 1991). The precise mechanisms that govern subunit assembly, especially the different combinations, are not well understood but depend on luminal interactions between the N-terminal domains (NTDs) of the subunits (Kuusinen et al. 1999). Tetramers form from dimers, which require the transmembrane segments and the extracellular S2 loop for assembly (Ayalon & Stern-Bach 2001). A recent study showed that interactions between the LBDs of the AMPARs subunits are critical for the dimer-to-tetramer transition (Greger et al. 2006). The NTD, which is not required for homomeric assembly, seems to play an important role in the preferential assembly of heteromers (Ayalon et al. 2005). GluR1/2 heteromers exit the ER rapidly, whereas GluR2/3 heteromers are retained longer in the ER. The GluR2 subunit has an arginine-based ER retention motif that consists of a single arginine residue (R607) in the transmembrane domain (Greger et al. 2002). As discussed above, this arginine is generated by RNA editing of the original sequence coding for glutamine. This residue is also critical for channel properties and confers calcium impermeability and a characteristic linear rectifying property to GluR2-containing AMPARs (Burnashev et al. 1992). Transgenic mice with impaired Q/R editing exhibit epileptic seizures and die within two weeks after birth (Brusa et al. 1995). The Q/R editing results in a stable pool of GluR2 subunits in the ER that exits more efficiently in a heteromeric complex. Knockout mice that lack GluR2 do form GluR1/3 heteromers, as well as GluR1 and 3 homomers, but these channels are poorly translocated to synapses (Sans et al. 2003). It is unclear how the Q/R site regulates ER retention, but a retention protein that binds to the edited site may be responsible. Recent studies have suggested that other editing sites also regulate secretory trafficking of AMPARs. A developmentally regulated editing site, R/G at position 743 in the S2 domain, governs whether GluR2 homomers will form. Following editing, the formation of homomers is precluded (Greger et al. 2006). In cell lines, the flip and flop forms of AMPARs seem to traffic differentially to the surface. Homomeric AMPARs of the flop form accumulate in the ER, whereas those of the flip form traffic efficiently to the cell surface (Coleman et al. 2006). As a caveat, many of these studies make use of transfected recombinant proteins in cell lines or in primary neurons, and therefore it is not clear if native AMPARs are similarly regulated. It would be interesting to know if RNA editing and ER retention/export are modulated by neuronal activity or other signaling pathways that could change the composition of active surface AMPARs.

PSD: postsynaptic density

AMPARs associate with the ER chaperones BiP and calnexin (Rubio & Wenthold 1999), and GluR2 colocalizes extensively with BiP in the ER (Greger et al. 2002). These or other unidentified chaperones may control ER retention. Researchers have identified many proteins that interact with the C termini of the AMPARs (see **Figure 1**) (Song & Huganir 2002), and some of these proteins may also regulate ER retention or exit (**Figure 3**). The GluR2 C terminus has a PDZ consensus motif (SVKI) that interacts with several PDZ domain–containing proteins, including the protein interacting with C kinase 1 (PICK1) (Xia et al. 1999), which appears to control AMPAR endocytosis and/or recycling but may also be necessary for the exit of GluR2 from the ER (Greger et al. 2002). Another PDZ interaction, that between the GluR1 C terminus (ATGL site) and SAP97 (synapse-associated protein 97) (Leonard et al. 1998, Rumbaugh et al. 2003), seems to occur in the ER (Sans et al. 2001). The SAP97-interacting region of GluR1 is necessary for correct synaptic targeting, but it is unclear if this is due to ER retention of the protein (Hayashi et al. 2000). Intriguingly,

TARPs: transmembrane AMPAR regulatory proteins

LTP: long-term potentiation

LTD: long-term depression

glutamate binding and ion permeation through the pore are also required for normal expression of AMPARs; ligand mutants that cannot bind glutamate, and pore mutants that block ion permeation, exhibit decreased surface/synaptic expression and are retained in the ER (Grunwald & Kaplan 2003). This suggests that there may be a surveillance mechanism in the ER that allows only correctly folded and active channels to exit.

Stargazin, a calcium channel γ-subunit homolog, seems to control AMPAR trafficking at multiple points during the secretory process (Nicoll et al. 2006). Stargazin was originally identified as the mutant gene in the Stargazer mouse, which exhibits profound cerebellar ataxia and epilepsy (Osten & Stern-Bach 2006). Stargazin and its closely related γ-3, γ-4, and γ-8 paralogs [collectively called TARPs (transmembrane AMPAR regulatory proteins)] interact directly with all the AMPAR subunits to promote their transport to the cell surface (Chen et al. 2000, Tomita et al. 2003) and to modulate channel function (Priel et al. 2005, Tomita et al. 2005). Stargazer cerebellar granule cells exhibit a striking lack of surface AMPARs, and a large portion of the intracellularly retained receptors exhibit immature glycosylation (Tomita et al. 2003). FRET studies suggest that stargazin and the AMPARs may first

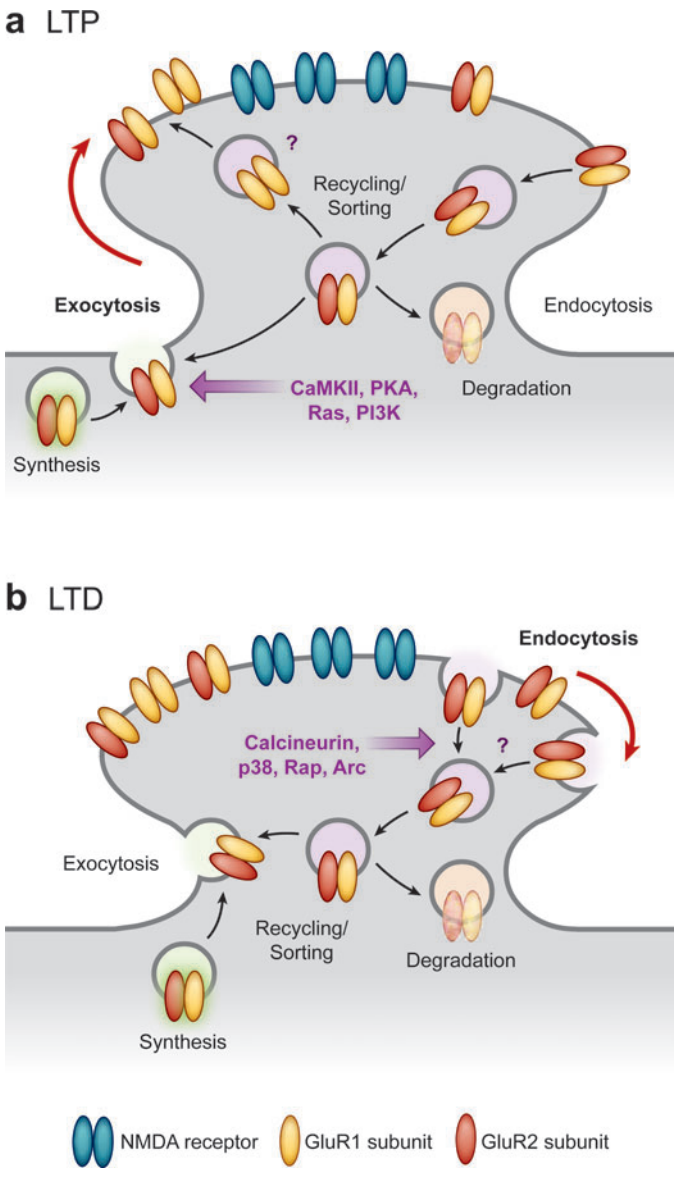


Figure 3

AMPA receptor (AMPAR) trafficking during synaptic plasticity. (*a*) AMPAR insertion occurs during long-term potentiation (LTP). Receptors are inserted at extrasynaptic sites or directly at the synapse. Extrasynaptic receptors diffuse into the synapse (*red arrow*), where they are trapped by scaffolding proteins such as PSD-95. It is unclear if receptors can be inserted directly at synapses. A recycling pool of receptors can provide a source for newly inserted receptors. A new finding suggests that GluR1 homomers are the first channels to be inserted during LTP, with a subsequent switch to GluR2 containing heteromers (Plant et al. 2006), although this finding remains controversial (see Adesnick & Nicoll 2007). Some kinases and downstream signaling molecules involved in LTP are listed in purple. CaMKII, calcium/calmodulin-dependent protein kinase II; PKA, protein kinase A; PI3K, phosphoinositide-3 kinase. (*b*) AMPAR endocytosis occurs during long-term depression (LTD). Most evidence suggests that receptors diffuse out (*red arrows*) of the postsynaptic density and are endocytosed at the lateral margins of spines. Internalized receptors are either sent to a recycling/sorting pool or degraded. Some kinases and downstream signaling molecules involved in LTD are listed in purple.

interact in the ER (Bedoukian et al. 2006). This suggests that stargazin may play a role in trafficking AMPARs from the ER to the *cis*-Golgi. In addition, stargazer granule cells exhibit an upregulated ER unfolded protein response (Vandenberghe et al. 2005), suggesting a role for stargazin in AMPAR folding or assembly. Mice lacking γ-8, the predominant hippocampal TARP, also exhibit dramatic intracellular retention of AMPARs in the ER and Golgi (Rouach et al. 2005), suggesting a conserved function. Stargazin is also able to alleviate the block in the ER exit of the flop isoforms in cell lines (Coleman et al. 2006), suggesting that stargazin may act as an escort chaperone. However, it is unclear if TARPS are absolutely required for correct AMPAR folding as an auxiliary subunit of the channel or whether they only enhance channel assembly. Further work is required to fully understand the role of TARPs in AMPAR folding and assembly during the biosynthetic process.

Biosynthesis in the Golgi

Neurons have both somatic and dendritic Golgi compartments, suggesting that proteins trafficking through the secretory pathway can exit in the soma or at specialized dendritic sites (Horton & Ehlers 2004). Indeed, these Golgi outposts may allow posttranslational modification of proteins that are locally translated in dendrites. All AMPAR subunits possess *N*-glycosylation sites but become fully glycosylated only in the Golgi. AMPARs have mostly complex oligosaccharide forms; they are relatively insensitive to treatment with Endo H (Rogers et al. 1991). nPIST, a protein enriched in the Golgi, dendritic tubulovesicles, and the postsynaptic density (PSD), interacts with the C-tail of stargazin and may help AMPARs exit the Golgi (Cuadra et al. 2004). Lipid modification of proteins also occurs in the Golgi. Recent studies have suggested that these modifications, especially palmitoylation, play important roles in synaptic function (El-Husseini et al. 2002, Huang & El-Husseini 2005). Palmitoylation is a reversible process that occurs by a covalent attachment of palmitate via thioester bonds to cytosolic cysteine residues. Protein palmitoylation is regulated by the balance of palmitoyl acyl transferase (PAT) and palmitoyl thioesterase activities. Palmitoylation of the scaffolding protein PSD-95 regulates AMPAR accumulation at synapses, and AMPAR internalization requires depalmitoylation of PSD-95 (El-Husseini et al. 2002). In addition, other AMPAR-interacting proteins important for membrane trafficking of the AMPARs, such as the glutamate receptor–interacting proteins GRIP1b and GRIP2b (pABP-L), are also palmitoylated (DeSouza et al. 2002, Yamazaki et al. 2001). A recent study showed that all the AMPAR subunits are palmitoylated at two sites and that these modifications are important for correct AMPAR trafficking (Hayashi et al. 2005). Palmitoylation occurs at a C-terminal cysteine that lies just after the final transmembrane domain and also at a cysteine in the TMD 2 region, three amino acids away from the Q/R editing site. Palmitoylation of this second site is increased by the Golgi apparatus–specific PAT GODZ [Golgi-specific DHHC (Asp-His-His-Cys) zinc finger protein], which promotes the accumulation of the receptor in the Golgi (Hayashi et al. 2005, Uemura et al. 2002). Palmitoylation of the C-terminal domain inhibits AMPAR interaction with the 4.1N protein, which stabilizes AMPAR surface expression (Shen et al. 2000). Mutation of the palmitoylation sites increases GluR1 association with 4.1N and inhibits the regulated endocytosis of AMPARs (Hayashi et al. 2005) (see below).

AMPA RECEPTOR TRAFFICKING

Neurons pose many unique problems for the trafficking of membrane proteins because of their highly polarized and elaborate structure. Membrane proteins must travel extremely long distances, and transmembrane proteins may be inserted at plasma membrane domains

far from their final location. Indeed, sites of synaptic contact contain their own milieu of proteins, and in some cases individual synapses contain specific receptor subtypes and scaffolding proteins that are different from their neighboring synapses only microns away.

Vesicular/Cytoskeletal Trafficking

Early in neuronal development, packets of receptors and scaffolding proteins travel along dendrites (Gerrow et al. 2006, Washbourne et al. 2002). The precise cues that govern where these receptors ultimately stop and form synapses are unknown. The trafficking of these packets is microtubule dependent, and transport is an active process involving motor proteins such as dynein and kinesin (Hirokawa & Takemura 2005). The multiple PDZ domain–containing protein GRIP1/ABP interacts directly with the heavy chain of conventional kinesin (KIF5) (Setou et al. 2002) and binds to the C-terminal PDZ motif of GluR2 and GluR3 (Dong et al. 1997). A complex of GluR2, GRIP1, and kinesin can be immunoprecipitated from brain lysates, and the expression of dominant-negative versions of kinesin decreases synaptic abundance of AMPARs (Setou et al. 2002). The kinesin KIF1 interacts with Liprin-α, which also interacts with the GluR2/GRIP1 complex (Wyszynski et al. 2002). KIF1 and AMPARs can be coimmunoprecipitated with KIF1 in brain lysates (Shin et al. 2003), and the expression of Liprin mutants that cannot bind GRIP1 blocks synaptic targeting of AMPARs (Wyszynski et al. 2002). These results indicate that the GRIP1/ABP protein serves as an adaptor to link AMPARs to kinesins and promote dendritic transport.

Although dendrites contain microtubules along which most cargo is transported, dendrites are also enriched in actin, especially in spines, which are small protrusions along dendrites that form small microcompartments important for synaptic function. Myosins, the main actin-dependent motor proteins, have recently been implicated in AMPAR transport. Myosin Vb has been associated with GluR1 (Lise et al. 2006), and the expression of the myosin Vb tail domain in developing hippocampal neurons enhances the accumulation of GluR1 in the soma but reduces the expression of GluR1 at the surface (Lise et al. 2006). Myosin VI has also been implicated in AMPAR trafficking (Osterweil et al. 2005). Myosin VI–deficient neurons exhibit deficits in activity-dependent AMPAR internalization as well as a decrease in the number of synapses and dendritic spines (Osterweil et al. 2005). Myosin VI is found in an AMPAR complex that includes the endocytosis adaptor protein AP-2 and the scaffolding protein SAP97, suggesting that Myosin VI may be selectively involved in clathrin-dependent endocytosis of AMPARs (Osterweil et al. 2005, Wu et al. 2002). Another actin adaptor, protein 4.1N, also associates with the AMPARs and appears to stabilize the surface expression of GluR1 (Shen et al. 2000). RIL (reversion-induced LIM protein), which has a PDZ domain, may also be involved in actin-dependent trafficking of GluR1 (Schulz et al. 2004). Live-imaging experiments of fluorescently tagged AMPARs have shown that GluR1 is constitutively and rapidly transported throughout the neuron. In contrast, GluR2 is less mobile and mostly retained in relatively immobile membrane-associated clusters, some of which are synapses. Interestingly, these receptor dynamics are independent of neuronal activity (Perestenko & Henley 2003).

Exocytosis

Precise synaptic targeting and insertion of receptors are extremely complicated, given that an average neuron contains approximately 10,000 synapses. Despite intense study, it is still unclear whether AMPARs are first inserted into the extrasynaptic plasma membrane or directly into synapses (see **Figures 2** and **3**). One possibility is that AMPARs first are inserted into the plasma membrane in the soma at extrasynaptic sites and then travel

out into dendrites via lateral diffusion in the plasma membrane until they finally reach the synapse and become anchored in the PSD. A recent study using an innovative method to measure receptor insertion of AMPARs has suggested that most receptors are inserted in the somatic plasma membrane (Adesnik et al. 2005). In this study, a membrane-impermeable photoreactive AMPAR antagonist derived from ANQX was used to photoinactivate surface receptors, and the subsequent exocytosis of AMPARs was then measured electrophysiologically. The recovery of synaptic receptors measured with this method was surprisingly slow, taking hours rather than minutes. In contrast, exocytosis of AMPARs in the soma was much faster. However, these data are inconsistent with many studies, including data from the same laboratory (Lu et al. 2001), that find more rapid insertion of receptors into the plasma membrane at dendrites and synapses. Another possibility is that AMPARs are trafficked intracellularly into dendrites via the cytoskeleton-associated motors and then directly inserted at synaptic sites. A recent study of the role of the exocyst complex in AMPAR delivery has suggested that Exo70 mediates AMPAR insertion directly within the PSD rather than at extrasynaptic membranes (Gerges et al. 2006). A third possibility is that AMPARs are synthesized in dendritic compartments and then inserted directly into synapses. Studies using cleavable extracellular-tagged transfected receptors suggest that AMPARs are inserted along dendrites (Passafaro et al. 2001) and that this occurs in a subunit-dependent manner. Other studies using different types of epitope tags, for example, a bungarotoxin-binding site or bi-arsenical dies, have observed similar dendritic insertion (Ju et al. 2004, Sekine-Aizawa & Huganir 2004). AMPAR insertion is blocked by the introduction of intracellular tetanus toxin, implying that AMPARs are inserted via SNARE-dependent exocytosis (Lu et al. 2001). Most likely a combination of all these processes occurs, depending on the subunit composition of the receptors and the context of the neuron's activity state.

Many studies have shown that plasma membrane insertion of AMPARs is dependent on the subunit composition of the receptor. Surface insertion of GluR1 and -4 (or the long-tailed AMPARs) occurs slowly in basal conditions and is stimulated by neuronal activity and NMDAR activation (Hayashi et al. 2000). In contrast, GluR2 insertion in many neurons is rapid and occurs constitutively under basal conditions, without the need for synaptic activity (Passafaro et al. 2001, Shi et al. 2001). Endogenous receptors consist mostly of either GluR1/2 or GluR2/3 heteromers, and the GluR1 trafficking signals dominate over GluR2 in controlling insertion. When GluR1/2 heteromeric channels are expressed, the activity-dependent trafficking of GluR1 dominates, whereas GluR2/3 heteromeric channels behave like GluR2 homomeric channels and constitutively traffic into the synapse. These subunit-specific rules for trafficking have led to a simple model in which GluR2-GluR3 receptors continuously cycle in and out of synapses, preserving the total number of synaptic AMPARs (the constitutive pathway), whereas GluR1-GluR2 (and GluR4) receptors are added into synapses in an activity-dependent manner during synaptic plasticity (the regulated pathway) (Malinow et al. 2000). The constitutive pathway may maintain synaptic strength despite protein turnover, and the regulated pathway may act transiently upon the induction of synaptic plasticity.

This differential trafficking of the AMPAR subunits is dependent on their C-terminal tails (see **Figure 1** for details). Expression of the C terminus of GluR2 decreases AMPA EPSCs, whereas expression of the GluR1 C terminus has no effect on the basal synaptic transmission but blocks activity-dependent increases in AMPA responses. The differential behavior of the tails seems to be governed by their interacting proteins. The GluR2 C terminus binds to *N*-ethylmaleimide-sensitive fusion protein (NSF) (Nishimune et al. 1998,

Osten et al. 1998, Song et al. 1998), and this site seems to regulate the rapid exocytosis of GluR2 at synaptic sites (Beretta et al. 2005). The mechanism by which NSF regulates AMPAR trafficking may relate to its classical role in controlling membrane fusion (Rothman 1994). However, NSF may also regulate the interaction of GluR2 with another interacting protein, PICK1 (Hanley et al. 2002). PICK1 may bind to and stabilize intracellular pools of GluR2 that may provide a ready source of receptors for quick membrane insertion (Gardner et al. 2005, Liu & Cull-Candy 2005, Steinberg et al. 2004). NSF binding may dissociate the GluR2-PICK1 complex (Hanley et al. 2002), thus allowing membrane insertion. However, the precise molecular role of NSF in regulating AMPAR insertion remains elusive.

Synaptic Targeting and Membrane Diffusion

AMPARs are concentrated at synapses, where they are precisely localized to efficiently mediate the response to glutamate released from presynaptic terminals. Whether or not AMPARs are inserted into the plasma membrane at extrasynaptic regions or more locally at synapses, there must be molecules that retain the receptors at synapses to maintain the high density of receptors at the synapse. The molecular mechanisms underlying the synaptic retention of AMPARs are not clear, but AMPAR-interacting proteins seem to be critical in this process (Song & Huganir 2002). Indeed, PSD-95 and other members of the PSD-95 protein family are critical determinants for synaptic targeting of AMPARs. Overexpression of PSD-95 enhances AMPAR-mediated synaptic currents (Beique & Andrade 2003, El-Husseini et al. 2000). Moreover, knocking out or knocking down PSD-95 and its family members decreases the synaptic levels of AMPARs (Beique et al. 2006, Elias et al. 2006). Although PSD-95 does not directly interact with AMPARs, it does bind to stargazin and other members of the TARP family (Chen et al. 2000, Tomita et al. 2005), which provide the link to AMPARs. TARPs bind to all four AMPAR subunits and also interact through their C-terminal domains with the PDZ domains of PSD-95. This interaction between the TARPs and PSD-95 appears to be crucial for AMPAR targeting to synapses (Chen et al. 2000, Tomita et al. 2005). Another family of AMPAR-interacting proteins that has been reported to be involved in the synaptic retention is the neuronal pentraxins, NARP, NP1, and NPR (Song & Huganir 2002). These multimeric proteins bind to all AMPAR subunits and promote clustering of the receptor (O'Brien et al. 1999, 2002; Xu et al. 2003). Overexpression of NARP in neurons increases the number of synaptic AMPARs, and the expression of dominant-negative forms of NARP decreases AMPAR clusters (O'Brien et al. 1999, 2002).

How these AMPAR-interacting proteins promote the retention of receptors at synapses is not clear, but it is likely that they reduce the lateral membrane diffusion and endocytosis of the receptors. PSD-95 and stargazin presumably stabilize receptors by linking the receptors with the PSD. In contrast, the multimeric pentraxins likely link the receptors with extracellular proteins stabilizing the receptors at synapses. To test the mobility of receptors at synapses, the real-time lateral diffusion of surface AMPARs in the plasma membrane has recently been investigated directly by optical monitoring of the movement of single receptors, which relies on the use of small latex particles or quantum dots coupled via antibodies to the AMPAR extracellular domain (Borgdorff & Choquet 2002, Tardin et al. 2003). These studies showed that, whereas extrasynaptic AMPARs are highly mobile, synaptic AMPARs are relatively immobile under basal conditions. Neuronal activity significantly increases the movement of AMPARs, especially in extrasynaptic regions. Extrasynaptic receptors continuously move with high (10^{-1}–10^{-2} μm^2 s^{-1}) and low (less than 10^{-4} μm^2 s^{-1}) diffusion rates and

transiently interact with scaffolding protein clusters at synaptic sites. Receptor movements between scaffold clusters were Brownian in nature, moving in random steps. This indicates that scaffold proteins may act as molecular determinants of receptor exchange between extrasynaptic and synaptic membrane compartments. As discussed above, PSD-95 and stargazin are ideally suited for this role; together they interact with AMPARs but also bind to many other PSD proteins via multiple PDZ interactions in a scaffold-like manner. Recently the interaction between stargazin and PSD-95 has been shown to be crucial for AMPAR diffusion in and out of synapses (Bats et al. 2007). Disruption of this interaction led to an increase in AMPAR diffusion and prevented AMPAR accumulation at synaptic sites (Bats et al. 2007). This result indicates that the stargazin–PSD-95 complex limits AMPAR lateral diffusion at synapses and is critical for the retention of receptors at synapses.

Endocytosis

Clathrin-mediated endocytosis is a general mechanism of membrane protein regulation, and the core endocytic protein machinery is highly conserved in most species and cell types (Mousavi et al. 2004). Some of these proteins, such as dynamin and endophilin, are essential for endosome formation, whereas others, such as AP-2, act as clathrin adaptor molecules that link specific cargo with the clathrin lattice. However, many of these proteins also serve specific roles in specialized endocytic pathways such as synaptic vesicle recycling in the presynaptic nerve terminal. The classic dynamin mutation, *shibire*, causes paralysis because of a severe defect in synaptic vesicle recycling at the neuromuscular junction (Poodry et al. 1973).

Postsynaptic endocytosis of receptors is thought to be mediated by a similar repertoire of proteins, although perhaps via specific protein isoforms. Dynamin 2 and 3 are mostly postsynaptic and are localized to the PSD via their interaction with the postsynaptic scaffolding proteins Shank and Homer, respectively (Gray et al. 2003, Okamoto et al. 2001). Distinct isoforms of endophilins (2 and 3) are localized to postsynaptic membranes, whereas endophilin 1 is localized predominantly presynaptically (Chowdhury et al. 2006). Endocytosis of AMPARs is similar to the stimulated endocytosis of G protein–coupled receptors in that both processes occur via clathrin-coated pits and require dynamin. Numerous methods of blocking clathrin-dependent endocytosis, such as the expression of a dominant-negative form of dynamin, high concentrations of sucrose, or peptide-mediated disruption of the dynamin-amphiphysin complex, all block AMPAR endocytosis (Carroll et al. 1999a, Man et al. 2000, Wang & Linden 2000). After internalization, AMPARs are sorted either (*a*) within early endosomes to a specialized recycling endosome compartment that allows quick reinsertion to the surface or (*b*) to late endosomes and lysosomes that allow degradation (Ehlers 2000, Lee et al. 2004).

Specific endocytic zones, segregated from the PSD, can be found in the lateral margins of excitatory synapses (Blanpied et al. 2002). These sites appear to be sites of glutamate receptor internalization (Racz et al. 2004). This is particularly evident in electron micrographs of dendritic spines, which show the presence of clathrin-coated pits and vesicles (Petralia et al. 2003, Spacek & Harris 1997). These studies also suggest that clathrin-mediated endocytosis varies during the development of neurons. Immature neurons are more abundant in dendritically localized clathrin pits, which are hot spots of rapid and repeated clathrin coat assembly and disassembly. In contrast, clathrin coats in mature dendrites are more stable but fewer in number.

Specific postsynaptic proteins are selectively involved in the endocytosis of AMPARs. The immediate early gene (IEG) CPG2 mediates both constitutive and activity-regulated glutamate receptor internalization (Cottrell et al. 2004) and localizes to the endocytic zone

of excitatory synapses. CPG2 knockdown disrupted constitutive AMPAR and NMDAR internalization as well as activity-induced AMPAR internalization. Another IEG, Arc, is induced by neuronal activity associated with cognition and long-term forms of synaptic plasticity. Arc mRNA is exquisitely regulated: The transcribed message is targeted to the dendrites of neurons as they engage in information processing and storage, and it is locally translated at activated synapses (Steward & Worley 2001). Arc regulates AMPAR trafficking by interacting with the integral endocytic proteins dynamin and endophilin (Chowdhury et al. 2006, Rial Verde et al. 2006). High levels of Arc accelerate AMPAR endocytosis and decrease surface and synaptic AMPAR levels. These effects are specific to AMPARs, suggesting that Arc acts as an adaptor protein that localizes AMPARs to the endocytic machinery. These recent studies elucidate some of the specific protein machinery involved in AMPAR endocytosis, but the signals that regulate them still remain relatively unknown. The elucidation of these signals will be critical for understanding AMPAR trafficking because activity-dependent endocytosis of AMPARs leads to several forms of synaptic plasticity (see below).

Recycling

Recent studies suggest that recycling endosomes contain a pool of AMPARs that is a source for the rapid insertion of receptors. Activation of NMDA receptors can regulate the kinetics of recycling and significantly affect the relative amount of receptors that are maintained intracellularly versus on the surface (Park et al. 2004). This is particularly evident after long-term potentiation (LTP)-inducing stimuli, for which an increase in the general recycling of endocytic cargo occurs and recycling endosomes physically translocate into spines (Park et al. 2004, 2006). This enhancement of recycling also provides additional lipid membrane, which is critical for the structural growth and expansion of dendritic spines during LTP (Park et al. 2006). The coupling of AMPAR insertion and membrane addition may be an explanation for the tightly correlated scaling of spine size with AMPAR-mediated synaptic currents (Matsuzaki et al. 2001). The specific molecular players that regulate recycling are beginning to be elucidated, although precisely how NMDA activity regulates recycling remains unclear. One protein, NEEP21 (neuron-enriched endosomal protein of 21 kDa), is localized to early and recycling endosomes (Steiner et al. 2002) and interacts with general endocytic/recycling proteins such as syntaxin 13 (Prekeris et al. 1998). Downregulation of NEEP21 leads to impaired recycling of internalized transferrin receptor (Steiner et al. 2002) and neurotensin receptor 2 (Debaigt et al. 2004), suggesting a general role in receptor recycling. However, suppression of NEEP21 also significantly retards GluR1 and GluR2 recycling following NMDA-induced internalization (Steiner et al. 2002), which may occur through the interaction of NEEP21 with GRIP and syntaxin 13 (Steiner et al. 2005). These results suggest that the AMPAR-interacting proteins GRIP and PICK1 may play some role in the regulation of receptor recycling to modulate the level of synaptic receptors.

Degradation

Little is known about how AMPARs are degraded at synapses, but recent studies suggest a role for the ubiquitin/proteasome system (UPS). The UPS consists of a number of proteins that coordinately regulate many cellular functions, including protein degradation and endocytosis. Ubiquitination can signal endocytosis to occur through specialized machinery that regulates clathrin endocytosis, and it has been implicated in the trafficking of receptor tyrosine kinases (Mukhopadhyay & Riezman 2007). Generally, monoubiquitination signals endocytosis, whereas polyubquitination ultimately leads to degradation via the proteasome. However, monoubiquitination also seems to play a role as a sorting

signal that targets its substrates to multivesicular bodies, which is the first step leading to lysosomes, where degradation can also occur.

Initial studies in *Caenorhabditis elegans* found that direct ubiquitination of GLR-1 glutamate receptors (the AMPAR homologs) at synapses induced the removal of receptors from the postsynaptic membrane, a process that required the clathrin adaptor AP180 (Burbea et al. 2002). Loss-of-function mutants in the multisubunit APC ubiquitin ligase complex exhibit increased levels of GLR-1 (Juo & Kaplan 2004). A similar phenotype is observed at the neuromuscular synapse of *Drosophila* APC mutants, which also have increased postsynaptic glutamate receptor clustering and defects in synaptic transmission (van Roessel et al. 2004). GLR-1 does not seem to be a direct substrate of the APC, but the mutant phenotype can be suppressed by the introduction of a loss-of-function allele of the *AP180*, suggesting that APC activity is linked to the endocytic pathway (Juo & Kaplan 2004). Recently, the neuronal BTB-Kelch protein KEL-8 was identified as another player in the regulation of GLR-1 (Schaefer & Rongo 2006). KEL-8 mutants also exhibit increased GLR-1 clustering, and the phenotype is rescued by a loss of function of AP180. KEL-8 biochemically purifies with the cullin protein CUL-3, which is part of the large SCF ubiquitin ligase complex, suggesting that GLR-1 degradation occurs through this pathway (Schaefer & Rongo 2006).

The role of the UPS in the trafficking of AMPARs in mammalian neurons is less clear. Direct ubiquitination of AMPARs has not been observed, although the ubiquitination of AMPAR-interacting proteins occurs and seems to be important for AMPAR trafficking. Direct ubiquitination of PSD-95 by the ubiquitin ligase Mdm2 (Colledge et al. 2003) causes a loss of surface AMPARs. However, PSD-95 ubiquitination is not detectable in all conditions (Bingol & Schuman 2004, Ehlers 2003), possibly owing to subtle differences in experimental conditions. Other studies showed that the overexpression of ubiquitin mutated at lysine 48 (K48R), which occludes chain formation but allows monoubiquitination, prevents AMPA-induced receptor internalization (Patrick et al. 2003). The precise role of the UPS in AMPAR trafficking thus remains an important area of study.

AMPA RECEPTORS IN SYNAPTIC PLASTICITY

Changes in synaptic strength are thought to underlie memory storage in the brain (Martin et al. 2000). LTP and long-term depression (LTD) are the two most-studied and prevailing cellular models of synaptic plasticity (Malenka & Bear 2004). Multiple mechanisms serve different forms of LTP and LTD, with mechanisms differing across brain regions. However, in many cases changes in AMPAR levels have been implicated in the expression and maintenance of these forms of plasticity (see **Figure 3**). A full review of the LTP/LTD literature is beyond the scope of this article (for further reading, see Bredt & Nicoll 2003, Collingridge et al. 2004, Song & Huganir 2002). If left unchecked, LTP and LTD can saturate synaptic strength. Homeostatic plasticity may compensate for these forms of synaptic plasticity by scaling neuronal output without changing the relative strength of individual synapses, and this may occur through global changes in synaptic AMPARs (Turrigiano & Nelson 2004) (see **Figure 4**). In the sections below, we concentrate on the cellular and signaling processes that regulate AMPARs in the context of synaptic plasticity.

Long-Term Potentiation

Protein phosphorylation plays an important role in the regulation of neuronal function, as it does in almost all cell types (Greengard 2001). Protein kinases play integral roles in synaptic plasticity and have helped to elucidate many important signaling pathways involved in LTP and LTD (Thomas & Huganir 2004). Emerging evidence utilizing knock-in

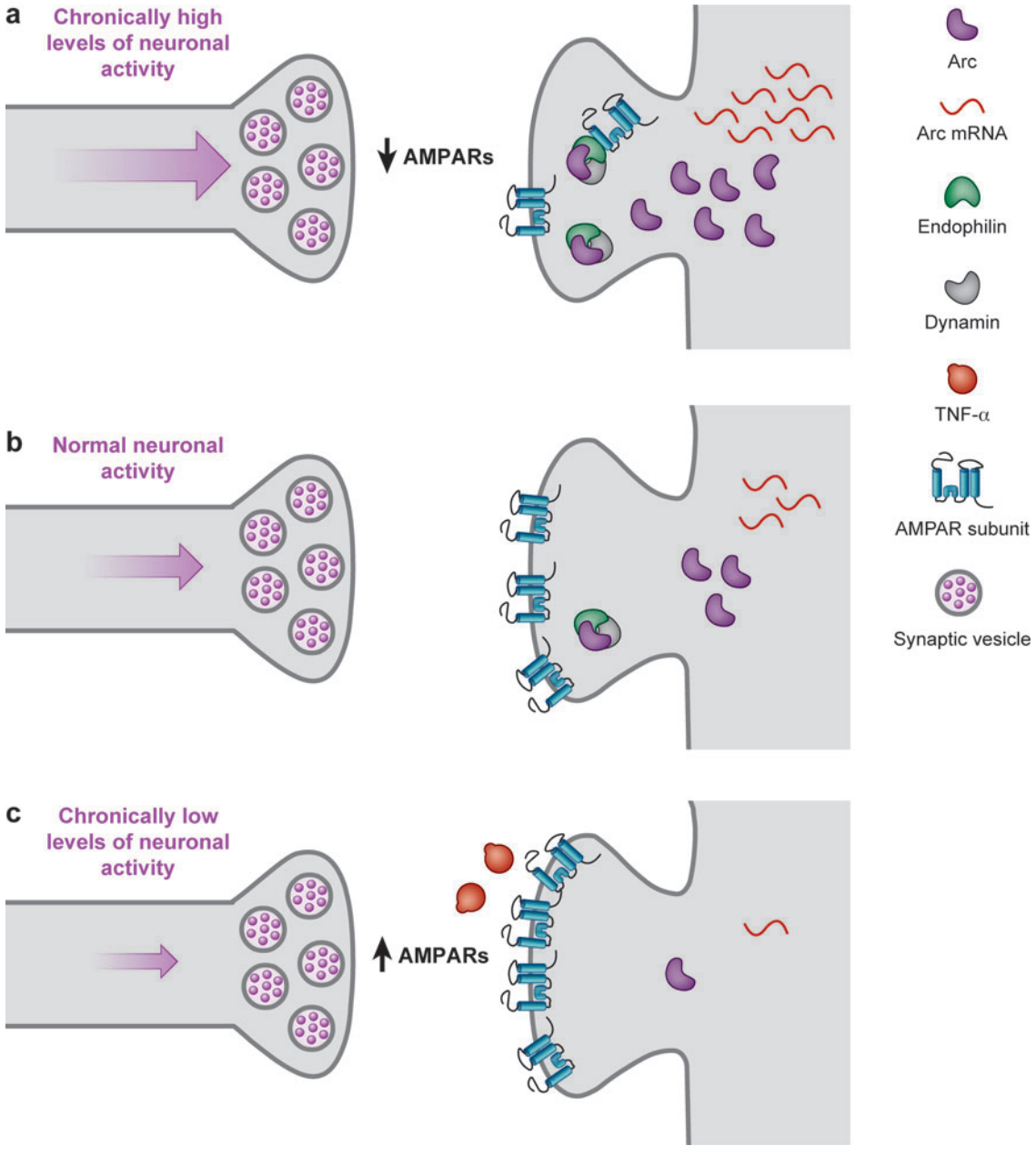


Figure 4

A model of homeostatic scaling of AMPA receptors (AMPARs). AMPARs are scaled in response to chronic changes in neuronal activity. (*a*) In conditions of persistent high activity, high levels of Arc are available to facilitate the endocytosis of AMPARs, with consequent downregulation of synaptic AMPARs. (*b*) At levels of normal neuronal activity, some Arc is expressed, and thus a constant level of surface AMPARs is homeostatically maintained. (*c*) In conditions of persistent low activity, during which Arc expression is dramatically reduced, Arc-dependent endocytosis is minimized, causing a shift in the steady-state AMPAR distribution toward membrane insertion. TNF-α is secreted by glia and also acts to increase AMPAR insertion.

mice has solidified the idea that the phosphorylation of AMPARs is critical for synaptic plasticity and memory (Lee et al. 2003, Steinberg et al. 2006). Many studies support a critical role for CaMKII in the induction of LTP (Lisman et al. 2002). Calcium influx through the NMDAR is crucial for the induction of LTP and results in CaMKII activation (Fukunaga et al. 1993). Postsynaptic injection of inhibitors of CaMKII, or genetic deletion of a crucial CaMKII subunit, blocks the induction of LTP (Malenka et al. 1989, Malinow et al. 1989, Silva et al. 1992). Moreover, the finding that intracellular perfusion of constitutively active CaMKII not only enhances the synaptic transmission but also occludes LTP (Lledo et al. 1995) strongly suggests a direct and causal role of CaMKII in LTP induction. CaMKII directly phosphorylates GluR1 at Ser831 (Barria et al. 1997a,b; Mammen et al. 1997), which increases AMPAR conductance (Benke et al. 1998). However, CaMKII does not seem to be required for synaptic delivery of receptors (Hayashi et al. 2000), although this site is phosphorylated during LTP (Lee et al. 2000).

Protein kinase A (PKA) phosphorylation of GluR1 at Ser845 is another critical event in LTP. Intracellular perfusion of PKA into GluR1-transfected HEK 293 cells resulted in a 40% potentiation of the peak amplitude of the whole-cell glutamate-gated current (Roche et al. 1996) and regulated the open-channel probability of the receptor (Banke et al. 2000). This potentiation was absent following the mutation of Ser845 to alanine. Pharmacological manipulations together with site-directed mutagenesis of Ser845 of GluR1 showed that phosphorylation of this site is necessary but not sufficient for the delivery of GluR1 to synapses during LTP (Malinow 2003). Ser845 phosphorylation may also induce AMPAR delivery to the extrasynaptic membrane and then to the synapse via surface diffusion (Man et al. 2007, Oh et al. 2006). The fact that LTP was diminished in a knock-in mouse in which Ser831 and Ser845 were mutated to prevent phosphorylation strongly supports a role of these phosphorylation sites in LTP (Lee et al. 2000).

GluR1 interactions seem to dominate the regulation of exocytosis during LTP. The PDZ ligand on GluR1 appears critical for activity-dependent trafficking of AMPARs because mutation of this site prevents the incorporation of GluR1 into spines (Piccini & Malinow 2002) and synapses (Hayashi et al. 2000, Kim et al. 2001). However, complete deletion of this PDZ ligand does not seem to inhibit LTP expression (Kim et al. 2001). In addition, surface expression and inducible exocytosis of GluR1 are impaired when the C terminus is mutated (Passafaro et al. 2001). It is postulated that LTP activates CaMKII, which then phosphorylates GluR1 and an unknown protein that in turn interacts with the PDZ motif of GluR1 (Hayashi et al. 2000, Shi et al. 2001). Because SAP97 is the only protein known to bind to the PDZ domain of GluR1, it will be of interest to examine further the possible role of SAP97 in LTP and determine if other scaffolding proteins can bind to the C terminus of GluR1.

Much of the work on AMPAR trafficking has involved the use of recombinant AMPARs. In most cases, these constructs form homomeric channels that allow for the study of subunit specificity in trafficking, but do not elucidate the regulation of endogenous heteromeric channels. Recent experiments have shown that endogenous AMPARs can be driven into the synapse during LTP (Shi et al. 2001) and by experience (Takahashi et al. 2003). Insertion requires C-terminal interactions; expression of the GluR1 C-tail prevents LTP and the experience-dependent delivery of AMPARs. Consistent with this, mature GluR1-knockout mice lack LTP in the CA1 region of hippocampus (Zamanillo et al. 1999), and the defect is rescued by genetically expressing GluR1 (Mack et al. 2001). However, these same mature mice still show some LTP in the dentate gyrus (Zamanillo et al. 1999) and also show LTP in the CA1 region in young mice (Mack et al. 2001), which indicates that GluR1-independent LTP also

exists. GluR4, which shares similarities with GluR1 in its C-terminal tail, may substitute for GluR1 in younger animals (Zhu et al. 2000).

Long-Term Depression

Many studies show that LTD results from the endocytosis of surface AMPARs (Beattie et al. 2000, Lissin et al. 1999). However, AMPAR internalization can occur in response to many stimuli (Ehlers 2000, Lin et al. 2000, Man et al. 2000), which has made the precise molecular pathways that underlie LTD difficult to isolate. Because most of these studies were performed in cultured cells, it is hard to know which pathways occur in vivo and which signaling molecules are the most important.

The first experimental support for the role of AMPA endocytosis in LTD came from immunocytochemical data, which showed that NMDAR-dependent chemical LTD in hippocampal cultures caused a decrease in the number of synapses containing surface AMPARs (Carroll et al. 1999b). Furthermore, hippocampal LTD induced in vivo caused a decrease in the number of AMPARs in synaptoneurosomes (Heynen et al. 2000). CA1 pyramidal neurons or cerebellar Purkinje cells loaded with a peptide that disrupts dynamin function blocked LTD (Luscher et al. 1999, Wang & Linden 2000). The inhibition of endocytosis also blocked the actions of insulin, which can cause a depression of synaptic currents that occludes LTD (Lin et al. 2000, Man et al. 2000). Indeed, the activation of NMDARs (Beattie et al. 2000, Carroll et al. 1999a, Ehlers 2000), mGluR receptors (Snyder et al. 2001, Xiao et al. 2001), or insulin receptors (Lin et al. 2000, Man et al. 2000) can cause a loss of synaptic/surface AMPARs. NMDA-induced AMPAR endocytosis resembles LTD: It requires calcium influx and activation of the calcium-dependent phosphatase calcineurin (Beattie et al. 2000, Ehlers 2000, Zhou et al. 2001).

Regulation of the phosphorylation of AMPAR subunits is also important for LTD expression. During hippocampal LTD, the PKA site on GluR1, Ser845, is dephosphorylated, whereas LTD induction in previously potentiated synapses leads to dephosphorylation of the CaMKII site, Ser831 (Lee et al. 2000). Mice that have these two sites mutated exhibit major deficits in LTD and AMPAR internalization induced by NMDAR activation (Lee et al. 2003). The mechanism by which the phosphorylation state of GluR1 affects AMPAR internalization is unknown but may involve differential regulation of AMPAR binding partners.

The interactions of GluR2 with several proteins are also involved in LTD. The clathrin adaptor protein AP-2 interacts with a site that overlaps with the NSF-binding site on GluR2, and this interaction is critical for NMDA-induced internalization of AMPARs (Lee et al. 2002). Moreover, the application of a peptide that specifically blocked the GluR2-AP2 interaction blocked the induction of LTD (Lee et al. 2002). Recent studies have indicated that the GluR2-interacting proteins GRIP, ABP/GRIP2, and PICK1 (all of which bind via the extreme C-terminal PDZ domain) also play a critical role in AMPAR endocytosis and LTD. A mutant form of GluR2 that does not bind to GRIP/ABP in hippocampal neurons targeted appropriately to the surface, but its accumulation at synapses was significantly reduced when compared with wild-type GluR2 (Osten et al. 2000, Shi et al. 2001). These data suggest that AMPARs are stabilized at the synapse by the binding of GluR2-containing receptors to GRIP/ABP, perhaps by limiting their endocytosis or by increasing recycling of GluR2.

Studies of LTD in cerebellar Purkinje cells provide further complexity to the signaling pathways triggering AMPAR endocytosis. Cerebellar LTD requires the activation of protein kinase C (PKC) (Linden & Connor 1991), which is required to stimulate AMPAR internalization (Xia et al. 2000). Activation of PKC with a phorbol ester is sufficient to induce LTD and AMPAR internalization (Chung et al. 2000). Ser880 within the

GluR2 PDZ-binding site is phosphorylated by PKC, which prevents the association of GluR2 with GRIP and ABP (Chung et al. 2000; Matsuda et al. 1999, 2000) but promotes binding to PICK1 (Chung et al. 2000, Matsuda et al. 1999, Perez et al. 2001). Phosphorylation of Ser880 promotes internalization of AMPARs and decreases surface GluR2-containing receptors in both Purkinje neurons (Matsuda et al. 2000) and hippocampal neurons (Chung et al. 2000, Perez et al. 2001). Transfection of a GluR2 construct with a point mutation that prevents phosphorylation of Ser880 into Purkinje cells failed to rescue LTD in GluR2-knockout neurons (Chung et al. 2003). In addition, the expression of GluR2 constructs that mimic Ser880 phosphorylation prevents synaptic targeting of receptors, decreases transmission, and partially occludes LTD (Seidenman et al. 2003). Although hippocampal LTD is accompanied by phosphorylation of Ser880, PKC does not mediate the phosphorylation of Ser880 (Kim et al. 2001), and hippocampal LTD does not seem to require a direct role for PKC. This suggests that other kinases in the hippocampus may phosphorylate this site.

Some controversy exists over the precise roles of GRIP and PICK1 in AMPAR trafficking and plasticity, and we still lack an exact understanding of their molecular functions. Some of the confusion on their role in LTD may be due to cell-type-specific differences. In addition, each protein may play multiple roles in the delivery, stabilization, and removal of synaptic AMPARs.

Homeostatic Scaling

Experiments using chronic manipulation of neuronal activity levels in dissociated cultured neurons showed that raising activity by blocking inhibitory synaptic transmission markedly decreased the number of synaptic AMPARs and the size of the AMPAR EPSC (Lissin et al. 1998). Similar manipulations in spinal (O'Brien et al. 1998) or cortical (Turrigiano et al. 1998) cultures also decreased the amplitude of miniature AMPAR EPSCs. Conversely, the application of AMPAR antagonists for hours to days caused an increase in the surface expression of AMPARs at synapses (Liao et al. 1999, O'Brien et al. 1998) and a decrease in the proportion of anatomically defined silent synapses (Liao et al. 1999). Several recent studies have addressed the molecular mechanisms underlying AMPAR homeostatic synaptic scaling. Blocking neural activity by TTX (a voltage-gated sodium channel blocker) decreases glutamate release, causing the release of the cytokine TNF-α from glia cells, which leads to the upregulation of AMPAR-mediated synaptic events through an unknown mechanism that involves the insertion of AMPARs (Stellwagen & Malenka 2006). The IEG *Arc* has also been implicated in regulating AMPAR scaling (Shepherd et al. 2006). Arc protein acts as a proxy sensor of neuronal activity and is bidirectionally regulated by the manipulation of activity in cultures. High activity induces high levels of Arc protein, which accelerates the endocytosis of AMPARs, causing a uniform decrease in AMPAR surface expression and a decrease in mEPSC amplitude. In contrast, blocking neuronal activity decreases Arc protein levels and correlates with a uniform increase of AMPAR surface expression and mEPSC amplitudes. Arc overexpression blocks homeostatic synaptic plasticity induced by TTX treatment, and Arc KO hippocampal neurons exhibit virtually no scaling in either direction (Shepherd et al. 2006). Neuronal activity regulates many genes, and most likely many proteins are involved in regulating homeostatic plasticity (Turrigiano & Nelson 2004). It will also be intriguing to see how homeostatic plasticity mechanisms interact or interfere with LTP/LTD.

AMPA RECEPTORS AND DISEASE

Because AMPARs play such an integral role in brain function, it is not too surprising that

Aβ: β-amyloid peptide

the dysregulation of AMPAR function has been implicated in many neurological diseases. However, it is very difficult to ascertain if AMPAR dysfunction is the initial cause or eventual aftermath of a disorder. Here we review evidence that AMPAR dysfunction may be one of the first manifestations of synaptic dysfunction that underlies Alzheimer's disease (AD).

Alzheimer's Disease

AD results from progressive and seemingly irreversible loss of neuronal function, ultimately leading to cell death in specific populations of neurons. The relative contributions of neuronal/synaptic dysfunction versus the hallmark histopathological lesions and neuronal cell loss to the symptomology and progression of the disease are not clear. This ultimately has important implications for the development of therapeutic targets because treatments that target only one process may not stop the progression or alleviate all the symptoms of the disease. Synaptic dysfunction in AD is particularly important because it may underlie the cognitive deficits that characterize the disease and has remained relatively unexplored until recently (Small et al. 2001). The pathological hallmarks of AD include amyloid plaques, predominantly composed of aggregated β-amyloid peptide (Aβ), and neurofibrillary tangles composed of hyperphosphorylated tau protein. The Aβ peptide is derived from proteolytic cleavage of the amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase (presenilin is the catalytic component of this complex). The normal role of APP and Aβ in the brain has been one of the most puzzling problems for the Alzheimer's field, and even after years of effort this problem remains unsolved. However, emerging evidence suggests that Aβ is directly involved in modulating synaptic function and that pathological levels of Aβ inhibit synaptic plasticity. Studies from AD mouse models that express genes encoding mutant APP or presenilin linked to familial AD exhibit impaired memory and synaptic plasticity prior to the formation of plaques, suggesting that synaptic dysfunction rather than a loss of neurons underlies the initial development of the disease (Chapman et al. 1999, Hsia et al. 1999, Oddo et al. 2003). Furthermore, the application of oligomeric forms of Aβ adversely affects LTP and synaptic transmission (Walsh et al. 2002). Aβ secretion in vivo is modulated by neuronal activity and depresses both AMPA and NMDA currents in slices (Cirrito et al. 2005, Kamenetz et al. 2003, Snyder et al. 2005). The mechanism of Aβ-induced synaptic depression appears similar to signaling pathways involved in LTD (Hsieh et al. 2006). Indeed, Aβ overexpression decreases synaptic AMPAR number. Expression of an AMPAR mutant that is unable to endocytose in response to LTD stimuli blocks the synaptic depression induced by Aβ. Intriguingly, Aβ can also induce phosphorylation of AMPARs at Ser880, a site important for AMPAR endocytosis and LTD (Hsieh et al. 2006). How secreted Aβ can modulate AMPAR function through an intracellular signaling cascade remains a critical, unanswered question.

FUTURE DIRECTIONS

Great strides have been made in elucidating the molecular players that govern AMPAR trafficking, but we have little understanding about their detailed dynamics and the precise functional role that they play. Advances in imaging technology and better protein tags now allow direct observation of receptors in real time. The manipulation of neuronal activity has also become easier with the advent of two-photon uncaging of neurotransmitters and second messengers as well as advances in light-activated ion channels (Deisseroth et al. 2006). Many basic cell biological questions still remain to be addressed. What is the role of locally synthesized receptors, and how

are local translation and mRNA trafficking regulated? How do receptors traffic in and out of the entangled complex of proteins in the PSD? When does lateral diffusion versus direct insertion/internalization occur at synapses? In addition, a huge challenge remains to elucidate the role of AMPAR trafficking in vivo, in terms of precise mechanisms, as well as determine the role that these processes play in synaptic plasticity and behavior. Information can be stored in the brain for years, yet AMPARs are highly dynamic and have a metabolic half-life of only a couple of days. Therefore, if AMPAR levels do determine synaptic strength, how can synaptic weights be maintained for weeks, months, or years? Moreover, how do individual synapses within a neuron know how many receptors it needs to maintain its potentiated or depressed state? These questions and many more remain the domain of future investigations. The answers to these questions will have far-reaching implications for our understanding of how the brain functions and should also shed light on the many neurological and cognitive disorders.

SUMMARY POINTS

1. AMPA receptors (AMPARs), consisting of four different subunits that are also alternatively spliced and RNA edited, form tetrameric ion channels that mediate most excitatory neurotransmission.
2. Individual subunits can be synthesized in the cell body, with channel assembly occurring in the ER and posttranslational modifications such as palmitoylation occurring in the Golgi. Subunits can also be synthesized locally in dendrites from mRNA that is trafficked out from the cell body. Neurons contain polyribosomes, translational machinery, and Golgi outposts in dendrites.
3. The endocytosis, exocytosis, and recycling of AMPARs are highly regulated processes that involve general endocytic proteins such as dynamin but also require specific AMPAR-interacting proteins such as PICK1, GRIP, NSF, and Arc.
4. AMPARs are concentrated at synapses, where they are properly positioned to transduce synaptic signaling. The localization of AMPARs is critically dependent on several AMPAR-interacting proteins, including PSD-95 and the TARPs.
5. Models of synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD) require correct trafficking of AMPARs. LTP generally requires newly inserted AMPARs that are incorporated at synapses, and LTD results from the removal of synaptic AMPARs. Insertion and removal of AMPARs also regulate homeostatic scaling of AMPARs in response to chronic changes in neuronal activity.
6. Disruption of AMPAR trafficking can result in synaptic dysfunction. One example is dysfunction induced by β-amyloid peptide (Aβ) in Alzheimer's disease. Aβ induces synaptic depression and spine loss through mechanisms that are similar to those seen in LTD.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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