Neuron
Review

The Role of the GluR2 Subunit in AMPA Receptor Function and Synaptic Plasticity

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DOI 10.1016/j.neuron.2007.06.001

The AMPA receptor (AMPAR) GluR2 subunit dictates the critical biophysical properties of the receptor, strongly influences receptor assembly and trafficking, and plays pivotal roles in a number of forms of long-term synaptic plasticity. Most neuronal AMPARs contain this critical subunit; however, in certain restricted neuronal populations and under certain physiological or pathological conditions, AMPARs that lack this subunit are expressed. There is a current surge of interest in such GluR2-lacking Ca^{2+}-permeable AMPARs in how they affect the regulation of synaptic transmission. Here, we bring together recent data highlighting the novel and important roles of GluR2 in synaptic function and plasticity.

Introduction

In the mammalian central nervous system, AMPA-type glutamate receptors mediate the vast majority of fast excitatory synaptic transmission. AMPARs are tetramers made up of combinations of four subunits: GluR1, GluR2, GluR3, and GluR4 (also called "GluRA–D") (Borges and Dingledine, 1998; Dingledine et al., 1999). All AMPAR subunit proteins have an extracellular N terminus, an intracellular C terminus, and four membrane-associated hydrophobic domains (M1–4), one of which (M2) forms a re-entrant loop (Figures 1A and 1B). Stargazin or other transmembrane AMPAR regulatory proteins (TARPs) also coassemble stoichiometrically with native AMPARs. The TARPs act as auxiliary subunits that are required for AMPAR maturation, trafficking, and channel function (Chen et al., 2000; Nicoll et al., 2006; Rouach et al., 2005; Tomita et al., 2003, 2005; Ziff, 2007).

AMPARs are widely expressed throughout the central nervous system both in neurons and in glia (Belachew and Gallo, 2004; Wisden and Seeburg, 1993). The great majority of AMPARs in the central nervous system exist as heteromers containing GluR2 (Greger et al., 2002; Wenthold et al., 1996). For example, in forebrain, including hippocampus and cerebral neocortex, the predominantly expressed subunits are GluR1 and GluR2, with low levels of GluR3 and GluR4 (Craig et al., 1993; Geiger et al., 1995; Monyer et al., 1991; Sans et al., 2003; Tsuzuki et al., 2001). Thus, the major neuronal population, pyramidal cells, express AMPARs primarily comprised of heterotetramers of GluR1 and GluR2 (Sans et al., 2003; Wenthold et al., 1996). Although GluR2/3 has been hypothesized as the other major heteromer in cortical principal cells, expression of GluR3 is low in this cell type (~10% of GluR1 or GluR2 levels) (Geiger et al., 1995; Sans et al., 2003; Tsuzuki et al., 2001; Wenthold et al., 1996), suggesting that GluR2/3 heteromers are not a predominant subunit combination.

During early postnatal development, expression of GluR2 is low compared with that of GluR1, but it increases rapidly during the first postnatal week (Monyer et al., 1991; Wisden and Seeburg, 1993). Consistent with this, synaptic GluR2-lacking AMPARs can be detected during a restricted developmental period in neonatal layer V pyramidal neurons (Kumar et al., 2002) and at early days in vitro in dissociated hippocampal culture (Pickard et al., 2000). Since AMPARs lacking GluR2 are Ca^{2+} permeable (see below), this suggests that early in development, such receptors play a role in neonatal synaptic function. In addition, throughout the brain, GABAergic interneurons, which represent about 10% of the total cell population, exhibit low levels of GluR2 subunit expression, and several subpopulations of these neurons express a significant proportion of GluR2-lacking Ca^{2+}-permeable AMPARs at all developmental stages (Geiger et al., 1995; Koh et al., 1995a; McBain and Dingledine, 1993).

GluR2 and AMPAR Biophysics

GluR2 is a critical subunit in determining mammalian AMPAR function. This subunit determines many of the major biophysical properties of the native receptor, including, but not limited to, receptor kinetics, single-channel conductance, Ca^{2+} permeability, and block by endogenous polyamines. In addition, it is the most tightly regulated of the glutamate receptor subunits, with a number of specific regulatory processes at the level of gene expression, RNA editing, receptor assembly, and trafficking. Moreover, genetic manipulations of this subunit cause the most profound phenotype of all the AMPAR subunits, demonstrating the critical importance of GluR2 for normal brain function (Brusa et al., 1995; Feldmeyer et al., 1999; Gerlai et al., 1998; Hartmann et al., 2004; Higuchi et al., 2000; Shimshek et al., 2006a, 2006b). Most mature GluR2 protein contains an arginine residue (R) within the

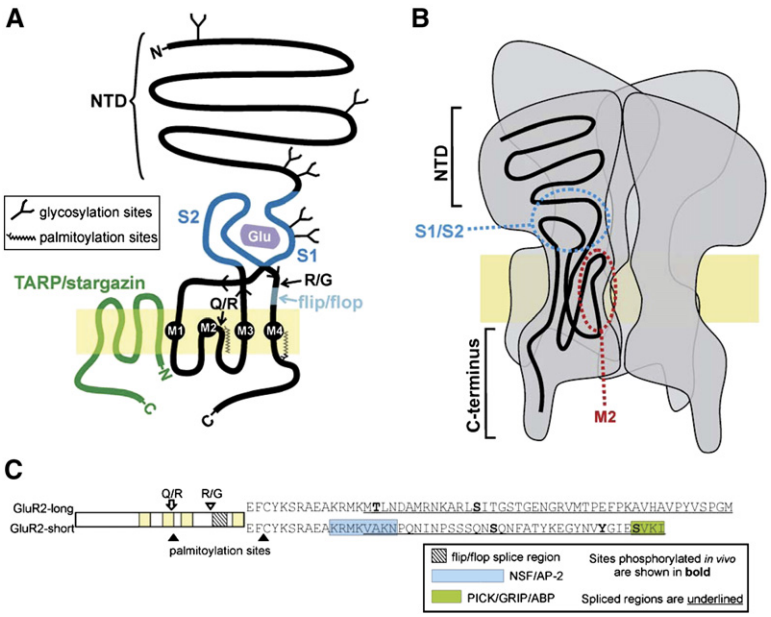

Figure 1. GluR2 Subunit Structure and General Structure of the AMPAR Complex

(A) Schematic of an AMPAR subunit in the plasma membrane. N-terminal domain (NTD), S1 and S2 ligand binding domains, membrane spanning domains (M1–4), Q/R and R/G RNA editing sites, flip/flop alternatively spliced region, glycosylation, and palmitoylation sites are indicated. The associated TARP/stargazin is also shown.

(B) Schematic of predicted 3D structure of the tetrameric AMPAR complex, with NTD, S1 and S2, M2, and C terminus regions indicated.

(C) GluR2 subunit domain structure with C terminus sequence detailed for the GluR2-short splice isoform (predominant form in the brain) and the GluR2-long isoform. Transmembrane domains indicated in yellow; flip/flop alternatively spliced region is shaded; editing, palmitoylation, phosphorylation, and protein interaction sites are as indicated.

re-entrant M2 membrane loop region at position 607 in place of the genomically encoded glutamine (Q) (Figures 1A and 1C) (Sommer et al., 1991). This change is the result of hydrolytic editing of a single adenosine base in the pre-mRNA to an inosine by the adenosine deaminase enzyme ADAR2 (Higuchi et al., 1993). This Q/R editing is specific to the GluR2 subunit; more than 95% of GluR2 mRNA transcripts are edited in postnatal brain.

The additional positive charge introduced into the pore by the presence of R607 prevents both the passage of divalent cations (including Ca^{2+}) and block by endogenous intracellular polyamines, and reduces single-channel conductance (Jonas and Burnashev, 1995; Swanson et al., 1997; Verdoorn et al., 1991). Thus, channels containing edited GluR2 subunits have a linear current-voltage relationship (Boulter et al., 1990), are impermeable to Ca^{2+}, and exhibit a relatively low single-channel conductance, while those lacking edited GluR2 are Ca^{2+} permeable, of higher conductance, and are inwardly rectifying due to a voltage-dependent block by endogenous intracellular polyamines (Bowie and Mayer, 1995; Geiger et al., 1995; Hestrin, 1993; Jonas et al., 1994; Kamboj et al., 1995; Koh et al., 1995b). However, although GluR2-lacking AMPARs exhibit significant Ca^{2+} permeability, they are less permeable to Ca^{2+} than NMDARs. For example, recombinant GluR1 homomers exhibit a $P_{Ca}/P_{Na,K}$ ratio of 2.3, compared with $P_{Ca}/P_{Na,K}$ of 3–17 for NMDARs (of various subunit compositions) and $P_{Ca}/P_{Na,K} < 0.1$ for GluR1/2 heteromers (Dingledine et al., 1999). In neurons, GluR2-containing AMPARs in principle cells exhibit a $P_{Ca}/P_{Na,K}$ ratio of ~0.1, while in interneurons where there are significant levels of GluR2-lacking AMPARs, $P_{Ca}/P_{Na,K}$ varies from 1.6–0.7 depending on cell type (Geiger et al., 1995). The GluR2-dependent biophysical parameters of inward rectification, block by external polyamine, and Ca^{2+} permeability show a dose-dependence for, and also are differentially sensitive to, the number of GluR2 subunits in the AMPAR complex (Washburn et al., 1997). Ca^{2+} permeability and external polyamine block go hand-in-hand and are both more sensitive to the presence of GluR2 subunits than inward rectification is. This indicates that the copy number of GluR2 within the complex can differentially regulate the GluR2-dependent biophysical properties of the AMPAR. The relevance of this for native receptors is unclear, however, since other work (see below) indicates that AMPARs assemble in preferred subunit combinations containing either two GluR2 subunits or no GluR2 subunits (Brorson et al., 2004; Greger et al., 2003; Mansour et al., 2001).

There are a number of polyamine derivatives and toxins (e.g., philanthotoxin, joro spider toxin, argiotoxin, 1-naphthylacetyl-spermine) that act as channel blockers of GluR2-lacking AMPARs (Blaschke et al., 1993; Bowie and Mayer, 1995; Herlitze et al., 1993; Toth and McBain, 1998; Washburn and Dingledine, 1996; Washburn et al., 1997). Polyamines and polyamine derivatives and toxins can block GluR2-lacking AMPARs when applied extracellularly and show good selectivity over GluR2-containing AMPARs; therefore, these reagents are useful in probing the GluR2 content of AMPARs (Kumar et al., 2002; Liu and Cull-Candy, 2000; Terashima et al., 2004; Toth and McBain, 1998). These drugs also block other polyamine-modulated receptors such as α7 nicotinic, kainate, and NMDARs, although they exhibit varying degrees of selectivity for GluR2-lacking AMPARs over these other channels (Washburn and Dingledine, 1996).

GluR2 and AMPAR Assembly

GluR2 plays a critical role in AMPAR assembly and trafficking. AMPARs are tetramers (Rosenmund et al.,

1998; Wu et al., 1996) formed in the endoplasmic reticulum (ER) as a dimer of dimers (Mayer, 2006). The initial stage of formation is the dimerization of two subunits that is dependent on the interactions in the N-terminal domain (NTD) (Ayalon and Stern-Bach, 2001). This is followed by a second dimerization step mediated by associations at the ligand binding and membrane domains, and this latter process is dependent on Q/R editing of GluR2 (Greger et al., 2003). The formation and stabilization of the tetramer is further promoted by NTD interactions.

In cells where GluR2 is highly expressed, the great majority of the AMPARs contain this subunit (Wenthold et al., 1996), and the preferred organization of receptor complexes containing GluR2 is a symmetrical heteromer (Mansour et al., 2001).

The assembly of AMPARs in the ER and subsequent ER exit is influenced by subunit-specific interactions and editing of GluR2, both at the Q/R and at a second ("R/G") site (Brorson et al., 2004; Greger et al., 2003, 2006; Greger et al., 2002). This regulated ER exit results in a large GluR2 pool in the ER of cell types that highly express this subunit (such as cortical pyramidal neurons), and this may serve to ensure that the great majority of AMPARs include GluR2. In certain other cell types exhibiting relatively low levels of GluR2 expression, such as cortical GABAergic interneurons (Jonas et al., 1994; Lambolez et al., 1996; Tsuzuki et al., 2001), the limited availability of GluR2 results in a significant fraction of AMPARs lacking GluR2. Importantly, some subpopulations of inhibitory interneurons assemble and express both GluR2-containing and GluR2-lacking AMPARs in a single cell. Of particular interest is that these two types of AMPARs can be differentially targeted to synapses receiving distinct afferent input (Toth and McBain, 1998). This would suggest that stringent mechanisms are in place to regulate the availability of the GluR2 subunit during synthesis and targeting of GluRs in these cell types. Finally, there is also evidence that even in cells expressing high levels of GluR2, a functionally relevant population of GluR2-lacking AMPARs can be surface expressed under certain conditions (e.g., Clem and Barth, 2006; Ju et al., 2004; Plant et al., 2006; Thiagarajan et al., 2005). This may specifically relate to GluR1 homomers produced by local dendritic synthesis of this subunit (Ju et al., 2004; Sutton et al., 2006), potentially suggesting a differential assembly and trafficking for local dendritically synthesized AMPAR subunits.

GluR2 Interacting Proteins

Mechanisms exist in neurons for the subunit-specific trafficking of AMPARs to synapses (Collingridge et al., 2004; Malinow and Malenka, 2002). This is most well-explored for GluR1 and GluR2: for example, recombinant GluR2 homomers, when overexpressed in CA1 pyramidal neurons in hippocampal slices, are constitutively incorporated at synapses, while GluR1 homomers require LTP to produce their synaptic expression (Hayashi et al., 2000; Shi et al., 2001). Moreover, for coexpressed GluR1 and GluR2, GluR1 C-terminal-dependent mechanisms regulate the GluR1/2 heteromer (Shi et al., 2001). This differential subunit-dependent regulation involves protein-protein interactions with the C terminus of the AMPAR subunits. Many of these C-terminal AMPAR interactions are subunit specific, and the largest number of direct protein interactions has been described for GluR2. These are involved in a rapid subunit-specific regulation of GluR2-containing AMPARs, thus providing a mechanism by which AMPARs can be differentially trafficked depending on their GluR2 subunit composition. The best functionally characterized of these GluR2 interactions are at the proximal N-ethylamide-sensitive fusion protein (NSF) / adaptor protein 2 (AP2) site, and at the distal PDZ binding site.

NSF/AP2 Site

NSF, an ATPase required for membrane fusion events (Rothman, 1994), interacts directly with the C terminus of GluR2 (Nishimune et al., 1998; Osten et al., 1998; Song et al., 1998) (Figure 1C). This interaction is at a membrane proximal site via a novel binding motif (Nishimune et al., 1998), and α- and β-SNAPs can also coassemble with the GluR2-NSF complex (Hanley et al., 2002; Osten et al., 1998). AP2, a protein critical for clathrin-dependent endocytosis that acts as an adaptor for cargo to be internalized (Sorkin, 2004), also associates with GluR2 in the same region (Lee et al., 2002). The AP2 binding motif overlaps with, but is not identical to, the NSF binding site (Kastning et al., 2007; Lee et al., 2002).

Selective disruption of these interactions using peptides mimicking the binding sites shows that these binding partners are involved in the rapid regulation of AMPAR surface expression and function at synapses in hippocampal neurons. The GluR2-NSF interaction is required to maintain AMPAR expression at synapses (Lee et al., 2002; Luscher et al., 1999; Luthi et al., 1999; Nishimune et al., 1998; Noel et al., 1999; Song et al., 1998). The extent of the effect of blocking the GluR2-NSF interaction on synaptic AMPARs varies considerably between preparations: in culture, blockade of the interaction by viral expression of the peptide pep2m causes an almost complete loss of AMPARs from the surface of hippocampal neurons (Noel et al., 1999), while acute infusion of pep2m during patch-clamp recordings produces a reduction of ~35%–40% in AMPAR-mediated EPSC amplitude (Nishimune et al., 1998). This difference may be explained by the much shorter duration of the blockade in the acute infusion experiments, and the results in culture indicate that the GluR2-NSF interaction is required for synaptic expression of the great majority of AMPARs. The loss of synaptic AMPARs caused by blockade of GluR2-NSF binding prevents, and is reversibly occluded by, NMDAR-dependent LTD (Luscher et al., 1999; Luthi et al., 1999), indicating that the population of receptors regulated by this mechanism is involved in the expression of LTD. The role of the AP2-GluR2 interaction is less clear. One recent study reports that blockade of AP2-GluR2 binding causes an increase in AMPAR-mediated transmission (Kastning et al., 2007); however, an earlier study shows that blocking this

interaction has no effect on basal transmission but selectively prevents LTD (Lee et al., 2002). There is evidence that clathrin-mediated endocytosis regulates basal AMPAR function and is required for the internalization of AMPARs during NMDAR-dependent LTD (Carroll et al., 1999, 2001; Luscher et al., 1999). Therefore, one hypothesis is that AP2 recruits AMPARs for clathrin-mediated endocytosis during LTD in response to NMDAR-mediated Ca^{2+} influx. Recent work provides evidence that hippocalcin is a Ca^{2+} sensor involved in linking the NMDAR-mediated Ca^{2+} influx to the AP2-dependent internalization of AMPARs during LTD (Palmer et al., 2005).

PDZ Site Interactions

Three proteins, glutamate receptor interacting protein (GRIP) (Dong et al., 1997), AMPAR binding protein (ABP), also known as GRIP2 (Srivastava et al., 1998), and protein interacting with C-kinase-1 (PICK1) (Dev et al., 1999; Xia et al., 1999) interact with the extreme C terminus of GluR2 and GluR3, which contains a type II (Sheng and Sala, 2001) PDZ binding motif (Figure 1C). GRIP and ABP are structurally very similar and contain multiple PDZ domains, so they are capable of interacting with many of the same postsynaptic proteins. PICK1 contains a single PDZ domain but can dimerize via a separate BAR domain (Perez et al., 2001a). PICK1 also interacts with PKC, and it has been proposed that dimeric PICK1 can act to chaperone activated PKC to AMPARs (Chung et al., 2000; Perez et al., 2001a). The interaction of GRIP and ABP with GluR2 and PICK1 with GluR2 is dependent upon the phosphorylation state of serine 880 (S880), which is located in the PDZ ligand at the C terminus of GluR2; S880 phosphorylation prevents the GRIP/ABP interaction, but not the PICK1 interaction (Chung et al., 2000; Matsuda et al., 2000; Matsuda et al., 1999). In addition, ABP binding can itself prevent phosphorylation of S880 on the GluR2 C terminus (Fu et al., 2003). Phosphorylation of the tyrosine 876 (Y876) residue by Src tyrosine kinase also regulates the GRIP1/ABP interaction, but has no effect on PICK1 binding (Hayashi and Huganir, 2004). Both S880 and Y876 can be phosphorylated in vivo and the regulation of the protein-protein interactions by these mechanisms are thought to influence the trafficking of GluR2-containing AMPARs to and from synapses during synaptic plasticity (Chung et al., 2003).

Studies using acute infusion of peptides mimicking the PDZ binding ligand on C-terminal GluR2 into neurons provide evidence that the GRIP/ABP-, but not the PICK1-, GluR2/3 interaction can acutely regulate synaptic transmission and is required for the expression of hippocampal LTD (Daw et al., 2000; Li et al., 1999). However, other studies also provide evidence for a requirement for the PICK1-GluR2 interaction in hippocampal LTD that is dependent upon phosphorylation of S880 on GluR2 (Kim et al., 2001; Seidenman et al., 2003). Puzzlingly, although numerous labs have reported a requirement of GluR2/3 PDZ interactions in hippocampal LTD, this form of plasticity is still observed in both the GluR2 knockouts and the GluR2 and GluR3 double knockouts (Meng et al., 2003). Although a resolution to this major discrepancy in the mechanism of hippocampal LTD has as of yet to be provided, a much clearer picture exists for the role of GluR2-interacting proteins in cerebellar Purkinje cell LTD. A series of studies has shown that the PICK1-GluR2 interaction and the PKC-dependent phosphorylation of S880 on GluR2 are required for this form of LTD (Chung et al., 2003; Steinberg et al., 2006; Xia et al., 2000), and that cerebellar LTD is absent in GluR2 knockout mice (Chung et al., 2003).

N-Terminal GluR2 Interactions

Recent work demonstrates a role for GluR2 N-terminal protein-protein interactions in promoting spine and synapse formation. The first indication of such a role was the finding that GluR2 overexpression in culture increases spine density in hippocampal neurons, while knockdown of endogenous GluR2 expression reduces spine number (Passafaro et al., 2003). The increase in spine number is associated with an increase in mEPSC frequency, indicating that this mechanism also increases the number of functional synapses. The GluR2-dependent increase in spine and synapse number appears to be entirely mediated by the N terminus of GluR2 (Saglietti et al., 2007). The mechanism involves a direct interaction of the GluR2 N terminus with N-cadherin, suggesting that GluR2 promotes spine and synapse formation and stabilization by a structural interaction with the presynaptic terminal. In future work it will be of great interest to elucidate the physiological significance of this novel mechanism that can potentially directly link postsynaptic and presynaptic function.

GluR2-Lacking AMPARS in Interneurons

As described above, the presence of GluR2 in the AMPAR complex confers distinct biophysical properties to the receptor. Neurons have numerous mechanisms to enable the tight regulation of this subunit to ensure that at the great majority of synapses, GluR2-containing Ca^{2+}-impermeable AMPARs are expressed. Considerable interest, however, currently centers on GluR2-lacking Ca^{2+}-permeable AMPARs because they confer novel properties on synapses and are expressed in specific, restricted cell populations or under certain physiological conditions. The roles of such receptors in synaptic function, synaptic plasticity, and local circuits are now beginning to be elucidated, and this is the topic to which we now turn.

The most detailed early descriptions of the physiological role for native GluR2-lacking, Ca^{2+}-permeable AMPARs originate from studies of synaptic transmission onto local-circuit GABAergic interneurons. Cortical interneurons are critically important for the precision timing of principal cell action potential firing and coordinating the output of large ensembles of pyramidal cells. Given that interneurons are embedded in both feedforward and feedback cortical inhibitory circuits, the input and output of these cells must be tuned according to the role they play in a particular network (Jonas et al., 2004; McBain and Fisahn, 2001). Excitatory synaptic transmission onto interneurons typically possesses EPSCs with rapid rise

and decay times (Carter and Regehr, 2002; Geiger et al., 1997; Walker et al., 2002). For example, EPSCs onto dentate gyrus basket cells have quantal amplitudes of 160 pA (at −70mV) and decay time constants of ~400 μs (at 34°C). Unlike principal cell AMPARs, which are typically comprised of GluR1 and GluR2, AMPARs at the mossy fiber-basket cell synapse are comprised almost exclusively of GluR1 (Geiger et al., 1995). In addition to Ca^{2+} permeability and the block by polyamines, native AMPARs lacking GluR2 exhibit faster channel deactivation kinetics (Geiger et al., 1995) and enhanced single-channel conductance (Swanson et al., 1997), contributing to large, rapidly decaying EPSPs (Lawrence and McBain, 2003). Consistent with this idea, at interneuron synapses there is a striking correlation between the time course of the synaptic conductance and inhibition by the polyamine toxin (Walker et al., 2002). Under current-clamp conditions activation of these GluR2-lacking AMPARs results in rapid EPSPs (Geiger et al., 1997), which trigger action potential firing in a narrow temporal window with little jitter (Jonas et al., 2004; Lawrence et al., 2004; Lei and McBain, 2002; Vida et al., 2006), emphasizing the role these receptors play in precisely controlling spike timing.

Novel Short-Term Plasticity at Ca^{2+}-Permeable AMPARs

In addition to providing a mechanism for rapid synaptic signaling, Ca^{2+}-permeable, GluR2-lacking AMPARs impart a novel form of short-term plasticity at interneuron synapses that is entirely postsynaptic in origin. As described above, GluR2-lacking AMPARs are blocked by endogenous intracellular polyamines (Bowie and Mayer, 1995; Kamboj et al., 1995; Koh et al., 1995a). In neurons, a tonic block of the AMPAR pore by endogenous polyamines is relieved by repetitive activation of GluR2-lacking receptors (Rozov and Burnashev, 1999; Rozov et al., 1998; Toth et al., 2000), resulting in a use-dependent increase in current flow through the channel that confers a novel postsynaptic mechanism of short-term synaptic plasticity (Figure 2). This use-dependent relief of polyamine block is frequency dependent, requires multiple stimuli to reach a maximum, and differs depending on the receptor subunit composition of the GluR2-lacking AMPAR (Rozov et al., 1998). This short-term facilitation appears not to depend on Ca^{2+} permeation or ion flux through the receptor per se but arises entirely from a voltage- and use-dependent relief of block by internal polyamines (Bowie et al., 1998; Rozov et al., 1998). Facilitation of currents lasts only for a limited time before reblock of the channel occurs. The reblocking mechanism proceeds without requiring the channel to reopen, suggesting that polyamines do not act only as classical open channel blockers (Bowie et al., 1998; Rozov et al., 1998).

Although polyamines are important cytoplasmic constituents in many cell types, their free concentration has been hard to determine (Tabor and Tabor, 1984; Soulet and Rivest, 2003). Physiologically, their levels are tightly controlled by a number of enzymatic steps, chelated by cytoplasmic ATP, and strongly influenced by patterns of ongoing activity (Watanabe et al., 1991; Bowie and Mayer 1995). Pathophysiological conditions such as seizures, electrographic activity, and forebrain ischemia can also regulate intracellular polyamine availability (Hayashi et al., 1993; Zoli et al., 1993). Of particular relevance, in developing *Xenopus* optic tectum a brief episode of visual stimulation increases the rectification properties of Ca^{2+}-permeable AMPARs, resulting in an overall reduction in AMPAR-mediated drive at retinotectal synapses (Aizenman et al., 2002; 2003). This effect of visual stimulation is blocked by polyamine synthesis inhibitors, suggesting that visual activity directly regulates the polyamine synthetic pathway, which can then directly tune AMPAR function to influence the integrative properties of the retinotectal system. A similar scenario has been observed in developing rat cortex and hippocampus (Shin et al., 2005). Ornithine decarboxylase, a metabolic precursor for polyamines, is highly enriched in immature layer V pyramidal neurons when compared with those of the adult, suggesting that the levels of endogenous polyamines play a critical role in establishing the modulatory control of GluR2-lacking AMPARs in developing animals.

Novel Mechanisms of Long-Term Synaptic Plasticity Are Associated with GluR2-Lacking AMPARs

The first indication that novel forms of long-lasting synaptic plasticity could be observed at synapses bearing GluR2-lacking AMPARs came from studying excitatory transmission onto interneurons of the amygdala (Mahanty and Sah, 1998). There, an NMDAR-independent form of LTP was observed at synapses expressing GluR2-lacking AMPARs, whose induction requires a postsynaptic rise in Ca^{2+} levels, presumably (but not proven) to occur from Ca^{2+} entry through the GluR2-lacking AMPAR. Subsequent work on hippocampal interneurons described a number of forms of long-term synaptic plasticity at inputs expressing GluR2-lacking AMPARs. A novel form of mGluR7-dependent long-term depression occurs at synapses expressing GluR2-lacking AMPARs on hippocampal interneurons in the CA3 stratum radiatum and lucidum that requires a postsynaptic Ca^{2+} influx through GluR2-lacking AMPARs (Laezza et al., 1999; Pelkey et al., 2005; Toth et al., 2000). NMDAR-independent LTP has also been described at excitatory synapses containing GluR2-lacking AMPARs on hippocampal stratum oriens interneurons (Lapointe et al., 2004; Perez et al., 2001b). This form of plasticity is critically dependent upon metabotropic glutamate receptor function and is absent in the mGluR1 knockout mouse. Interestingly, this plasticity occurs only at synapses expressing GluR2-lacking AMPARs, but surprisingly does not appear to require Ca^{2+} flux through these receptors for induction or expression (Topolnik et al., 2005). Recently, Kullmann and colleagues (Lamsa et al., 2007) described a novel role for GluR2-lacking AMPARs in LTP at this same synapse. In a mechanism akin to the voltage-dependent unblock of Mg^{2+} from the NMDAR during classical NMDAR-dependent LTP, they demonstrate that

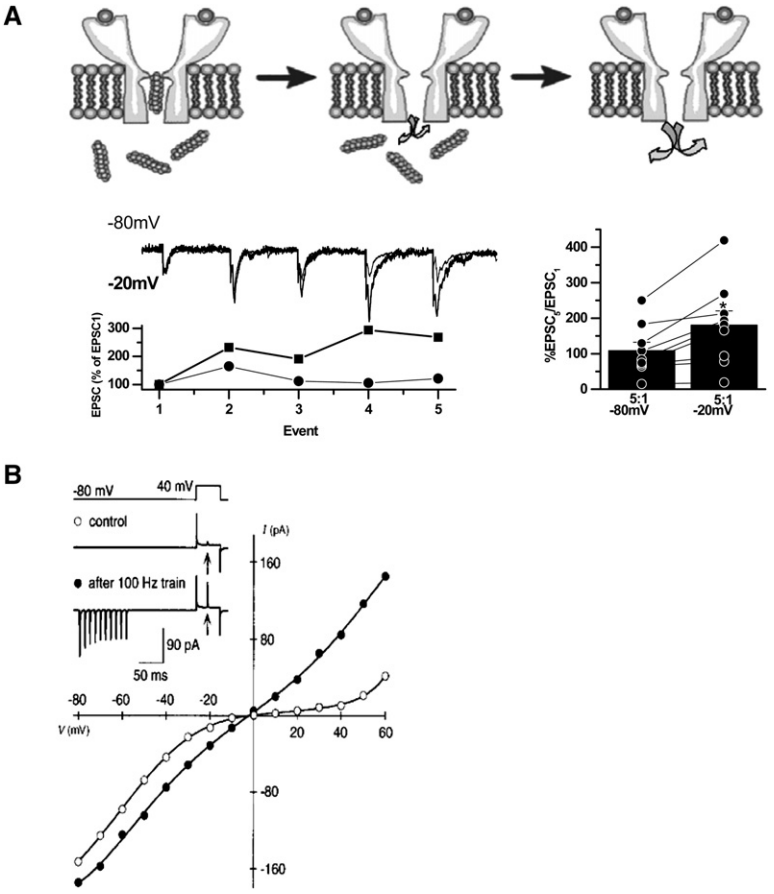

Figure 2. GluR2-Lacking AMPAR-Dependent Short-Term Synaptic Plasticity

(A) The upper panel schematic shows the mechanism of polyamine block of AMPARs. (Left) GluR2-lacking, Ca^{2+}-permeable AMPARs are tonically blocked by intracellular polyamines. Unblock of polyamines from the channel vestibule is use dependent (center) and typically requires repetitive synaptic stimulation to reach maximal current amplitude (right). (Lower panel) At mossy fiber-interneuron CP-AMPAR synapses, normalizing the first EPSCs in the train evoked at both −20mV and −80mV reveals a greater degree of facilitation in EPSCs evoked at −20mV. This voltage-dependent increase in the degree of facilitation at more positive potentials is consistent with the greater tonic block by polyamines of AMPARs held at depolarized potentials. Error bars represent SEM.

(B) High-frequency stimulation relieves AMPAR channels from polyamine block in recombinant channels. Currents in GluR-2(Q) channels were recorded with 25 μM spermine added to the intracellular solution. Current-voltage relationship for control (open circles) and facilitated currents (closed circles) is indicated. In control, glutamate was applied 20 ms after stepping the potential from −80mV to various test potentials (−80mV to +60mV) at 0.2 Hz. An identical voltage protocol was used for the facilitated currents except that a 100 Hz train (ten pulses) of glutamate was applied at −80mV (conditioning glutamate pulses) 160 ms before the step to the test potential. (Inset) Example recordings at a test potential of +40mV; arrows indicate glutamate application during the test step. For the *I-V* curves, smooth lines are fitted sixth (control) or eighth order polynomials, and each point represents the mean of ten sweeps.

The upper panel of (A) was kindly provided by Derek Bowie, the lower panel of (A) is taken with permission from Toth et al. (2000), and (B) is reproduced with permission from Rozov et al. (1998).

NMDAR-independent LTP at synapses expressing GluR2-lacking AMPARs is enhanced by *hyperpolarization* of the membrane potential and is absent when the cell is depolarized. The authors hypothesize that the hyperpolarization acts to unblock polyamines from the intracellular pore, facilitating current flow (and presumably increasing the driving force for Ca^{2+} entry) through the GluR2-lacking AMPAR to induce LTP. However, in the absence of current-voltage relationships made in the presence and absence of intracellular polyamines, it is hard to gauge how much additional unblock of the pore actually occurs via this manipulation since, at voltages around resting potential, there typically exists only a minimal degree of polyamine block (Bowie and Mayer, 1995). Moreover, this is probably not a mechanism available to all synapses expressing GluR2-lacking AMPARs, since LTP at such synapses onto interneurons of the stratum radiatum is NMDAR dependent and is *blocked* by hyperpolarization (Dingledine and Laezza, 2004; Laezza et al., 1999). Although much remains unexplored concerning the precise mechanisms and roles of these novel forms of long-term synaptic plasticity, GluR2-lacking AMPARs clearly endow synapses on GABAergic interneurons with novel and unexpected properties that are likely to be critical for the function of local inhibitory circuits.

GluR2-Lacking AMPARS and Homeostatic Synaptic Plasticity

Cortical pyramidal neurons undergo a homeostasis of synaptic strength that is dependent upon the total synaptic input onto the cell. This property, which is termed homeostatic synaptic plasticity or synaptic scaling, is distinct from input-specific Hebbian forms of synaptic plasticity (such as LTP), and is most readily induced in vitro by chronically blocking neuronal activity or glutamatergic transmission in cultured neurons (Turrigiano et al., 1998; Turrigiano and Nelson, 2004). Recent studies show that GluR2-lacking AMPARs are involved in the expression mechanism underlying the increase in AMPAR-mediated transmission that occurs during homeostatic synaptic

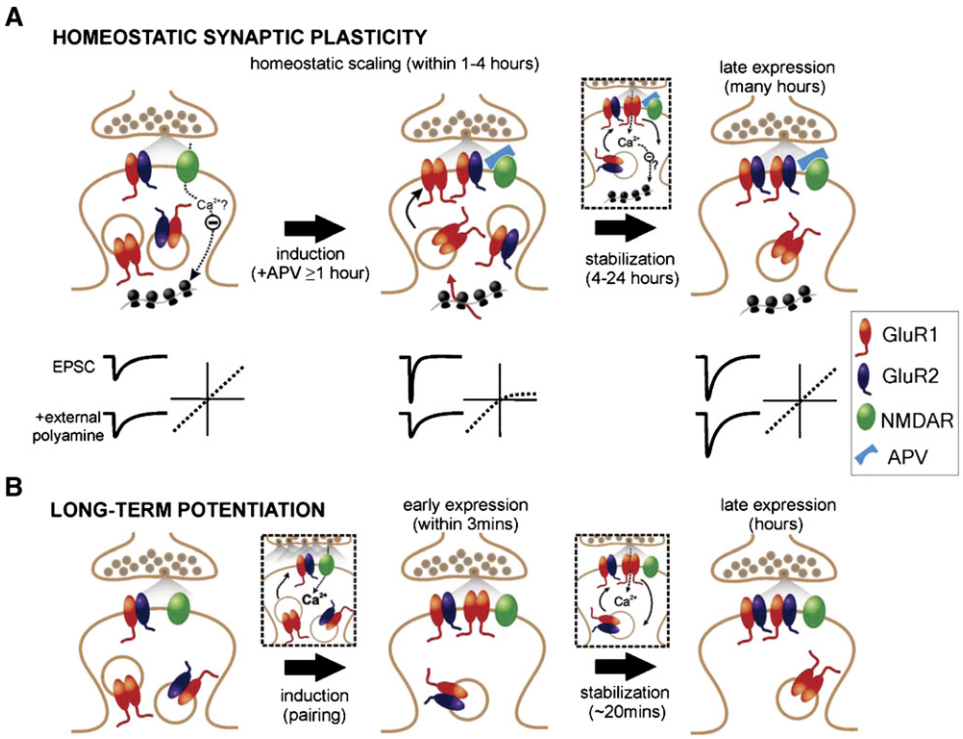

Figure 3. Comparison of Induction and Expression Mechanisms of Homeostatic Synaptic Plasticity and LTP in Hippocampal CA1 Pyramidal Neurons

In homeostatic synaptic plasticity (A), dendritic GluR1 synthesis is tonically suppressed by synaptic NMDAR activation (left); incubation of cultures or slices in D-APV for at least 1 hr relieves this suppression and leads to dendritic synthesis of GluR1 homomers and their incorporation at synapses to produce an increase in synaptic strength (middle). Stabilization of this synaptic strength change occurs over a longer time period (4–24 hr) and is associated with a replacement of GluR1 homomers with GluR2-containing AMPARs in a mechanism independent of NMDAR activation but possibly driven by Ca^{2+} influx through GluR2-lacking AMPARs (right). In LTP (B), transient strong activation of NMDARs produced during coincident pre- and postsynaptic activity causes a rapid incorporation of existing (already synthesized) GluR1 homomers into synapses within a few minutes of the induction stimulus (left, center). The increase in synaptic strength is stabilized over the next ~20 min by replacement of GluR1 homomers with GluR2-containing AMPARs in a mechanism independent of NMDAR activation and driven by Ca^{2+} influx through GluR2-lacking AMPARs (right). Biophysical changes in the AMPAR-mediated EPSC corresponding to the three states of synapses during these two forms of synaptic transmission are shown in the center.

plasticity. In response to chronic activity blockade, there is an increase in miniature EPSC amplitude that is specifically reversed by bath application of polyamine analogs or toxins (Ju et al., 2004; Sutton et al., 2006; Thiagarajan et al., 2005). This suggests that GluR2-lacking AMPARs are selectively incorporated at synapses to produce the synaptic scaling. Consistent with this, an increase in GluR1, but not GluR2, protein expression is observed in response to activity blockade, and this appears to be primarily due to a selective increase in dendritic protein synthesis of the GluR1 subunit (Ju et al., 2004; Sutton et al., 2006). Recent work indicates that NMDARs, activated during miniature synaptic events, actively inhibit dendritic GluR1 synthesis, tonically suppressing the synaptic expression of GluR1 homomers under control conditions; furthermore, blockade of NMDARs for as little as 1 hr can cause an increase in GluR1 synthesis and expression of GluR1 homomers at synapses (Sutton et al., 2006) (Figure 3A). However, following incorporation of these GluR2-lacking AMPARs, they are slowly replaced with GluR2-containing receptors over a period of 12–24 hr via a mechanism independent of NMDARs that maintains the increased synaptic strength (Sutton et al., 2006). Other work suggests that TNFα released from glia is required for homeostatic synaptic plasticity and insertion of GluR2-lacking AMPARs during activity blockade (Stellwagen et al., 2005; Stellwagen and Malenka, 2006). These findings thus indicate that GluR2-lacking AMPARs can be rapidly and locally synthesized and used to increase synaptic strength in response to changes in global activity in cortical pyramidal neurons. Such mechanisms may also occur in vivo: deprivation of sensory experience causes a global upregulation of synaptic transmission and an increase in GluR2-lacking AMPARs at synapses (Desai et al., 2002; Goel et al., 2006; Turrigiano and Nelson, 2004; Watt et al., 2000).

Homeostatic synaptic plasticity also requires Arc, the immediate early gene product that is strongly upregulated during activity and implicated in hippocampal learning and memory (Tzingounis and Nicoll, 2006). Arc overexpression

causes a reduction in evoked and miniature EPSC amplitude and reduced GluR2 surface expression (Chowdhury et al., 2006; Rial Verde et al., 2006; Shepherd et al., 2006). In synaptic scaling experiments, Arc activity is downregulated by chronic TTX treatment in culture, producing an increase in mEPSC amplitude, while synaptic scaling is absent in cultured neurons overexpressing Arc or in Arc knockout animals (Shepherd et al., 2006). These findings therefore demonstrate a requirement for Arc in homeostatic synaptic plasticity and indicate a potential role for Arc in regulating the GluR2 subunit composition of AMPARs that underlies the expression mechanism of this form of synaptic plasticity.

GluR2-Lacking AMPARs and Input-Specific Synaptic Plasticity

The GluR2 subunit is clearly important in the regulation of the induction of forms of long-term synaptic plasticity in principal neurons such as CA1 pyramidal neurons. Since the great majority of AMPARs in principal neurons contain GluR2, this renders AMPARs impermeable to Ca^{2+}, and the NMDAR or voltage-gated Ca^{2+} channels are the major pathways for synaptically evoked Ca^{2+} entry. In animals in which GluR2 is knocked out or in which GluR2 Q/R editing is altered, a major fraction of LTP is NMDAR independent (Feldmeyer et al., 1999; Jia et al., 1996), demonstrating the critical role played by GluR2 in determining the source of synaptic Ca^{2+} entry.

Recent work is now revealing an unexpected role for GluR2 in the expression of several forms of long-term synaptic plasticity involving the activity-dependent regulation of GluR2 subunit composition. Such a mechanism was first described for a novel form of synaptic plasticity at parallel fiber-stellate cell inputs in cerebellum, where Ca^{2+} influx through synaptic GluR2-lacking AMPARs during high-frequency activity produces a rapid switch to GluR2-containing receptors (Liu and Cull-Candy, 2000; 2002). Subsequently, it was demonstrated that this is mediated by a rapid subunit-specific trafficking of AMPARs involving the interactors PICK1, GRIP, and NSF (Gardner et al., 2005; Liu and Cull-Candy, 2005). Recent work shows that GluR2 subunit composition can also be regulated acutely during hippocampal LTP in CA1 pyramidal cells (Plant et al., 2006). LTP induction causes the rapid incorporation of GluR2-lacking AMPARs at synapses, but these are only present transiently, and are replaced by GluR2-containing receptors after ~20 min of LTP expression. Blockade of GluR2-lacking AMPARs during this early phase of expression causes a reversal of LTP, suggesting that Ca^{2+} influx through these receptors is necessary to drive the exchange for GluR2-containing receptors (Figure 3B). However, there is also evidence that LTP can be expressed and maintained without the involvement of this mechanism. Previous studies have shown no requirement for AMPAR activation in the maintenance of early LTP (Kauer et al., 1988; Muller et al., 1988). Moreover, a recent study reports that hippocampal LTP can be expressed without the transient incorporation of GluR2-lacking AMPARs (Adesnik and Nicoll, 2007). It is not clear why this study, which uses very similar experimental conditions, does not produce a similar GluR2 subunit composition switch to that reported in Plant et al. (2006). It is unlikely that technical or experimental issues explain the differences (for further discussion see electronic letter in response to Adesnik and Nicoll 2007 at http://www.jneurosci.org/cgi/eletters/27/17/4598), and more likely that the GluR2 subunit composition switch and the requirement for GluR2-lacking AMPARs for the early expression of LTP is not always required for hippocampal LTP. For example, it is possible that the requirement for the GluR2 subunit composition switch in LTP expression is developmentally regulated, dependent upon LTP induction protocol, or both. Elucidation of this issue will shed important light on the expression mechanism or mechanisms of LTP and the role of GluR2-lacking AMPARs in cortical pyramidal neurons.

There is accumulating evidence that synaptic plasticity in vivo uses similar GluR2-subunit-specific expression mechanisms. At layer 4 inputs onto layer 2/3 pyramidal cells in barrel cortex, a single whisker experience protocol, in which all whiskers but one are trimmed, causes a pathway-specific increase in synaptic strength and the incorporation of GluR2-lacking AMPARs in vivo (Clem and Barth, 2006). In other studies on the ventral tegmental area (VTA), an mGluR1-dependent form of LTD at glutamatergic synapses onto dopamine (DA) neurons has also been described, which causes a rapid switch from GluR2-lacking to GluR2-containing AMPARs (Bellone and Luscher, 2005). A similar mechanism can be activated in vivo by a single injection of cocaine into VTA, and there is evidence that this in vivo GluR2 subunit switch requires PICK1-GluR2 interactions (Bellone and Luscher, 2006).

These studies demonstrate a novel role for the GluR2 subunit in the expression of input-specific long-term synaptic plasticity. Although the precise roles of such Ca^{2+}-permeable AMPARs are currently unclear, these receptors will provide specific novel pathways for Ca^{2+} influx at synapses that could potentially act as a "tag" (Frey and Morris, 1997, 1998) for recently potentiated synapses that may be important for driving subsequent long-term changes in spine structure, local protein synthesis, and gene expression.

Conclusions

It is clear that GluR2 and its appropriate regulation is critical not only for many aspects of AMPAR function but also for normal brain function. This is most evident in transgenic mouse strains that lack either GluR2 itself or appropriate editing of this subunit. These animals exhibit a wide variety of profound detrimental phenotypes in synaptic function, development, and behavior (Brusa et al., 1995; Feldmeyer et al., 1999; Gerlai et al., 1998; Hartmann et al., 2004; Higuchi et al., 1993, 2000; Jia et al., 1996; Shimshek et al., 2006a, 2006b; Yan et al., 2002). Moreover, there is considerable evidence that disruption in GluR2 function is associated with a number of

neurological disorders such as cerebral ischemia, amyotrophic lateral sclerosis, pain, and epilepsy (Cull-Candy et al., 2006). Thus, mechanisms for the regulation of GluR2-subunit-containing AMPARs are of particular interest, and we are only now starting to appreciate the extent and roles of such processes in synaptic function and plasticity. This is likely to continue to be an important area of study for novel mechanisms regulating synaptic function in physiology and disease.

ACKNOWLEDGMENTS

This work was supported by the NINDS (J.T.R.I.) and NICHD (C.J.M.) Intramural Program.

REFERENCES

Adesnik, H., and Nicoll, R.A. (2007). Conservation of glutamate receptor 2-containing AMPA receptors during long-term potentiation. J. Neurosci. *27*, 4598–4602.

Aizenman, C.D., Munoz-Elias, G., and Cline, H.T. (2002). Visually driven modulation of glutamatergic synaptic transmission is mediated by the regulation of intracellular polyamines. Neuron *34*, 623–634.

Aizenman, C.D., Akerman, C.J., Jensen, K.R., and Cline, H.T. (2003). Visually driven regulation of intrinsic neuronal excitability improves stimulus detection in vivo. Neuron *39*, 831–842.

Ayalon, G., and Stern-Bach, Y. (2001). Functional assembly of AMPA and kainate receptors is mediated by several discrete protein-protein interactions. Neuron *31*, 103–113.

Belachew, S., and Gallo, V. (2004). Synaptic and extrasynaptic neurotransmitter receptors in glial precursors' quest for identity. Glia *48*, 185–196.

Bellone, C., and Luscher, C. (2005). mGluRs induce a long-term depression in the ventral tegmental area that involves a switch of the subunit composition of AMPA receptors. Eur. J. Neurosci. *21*, 1280–1288.

Bellone, C., and Luscher, C. (2006). Cocaine triggered AMPA receptor redistribution is reversed in vivo by mGluR-dependent long-term depression. Nat. Neurosci. *9*, 636–641.

Blaschke, M., Keller, B.U., Rivosecchi, R., Hollmann, M., Heinemann, S., and Konnerth, A. (1993). A single amino acid determines the subunit-specific spider toxin block of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate/kainate receptor channels. Proc. Natl. Acad. Sci. USA *90*, 6528–6532.

Borges, K., and Dingledine, R. (1998). AMPA receptors: molecular and functional diversity. Prog. Brain Res. *116*, 153–170.

Boulter, J., Hollmann, M., O'Shea-Greenfield, A., Hartley, M., Deneris, E., Maron, C., and Heinemann, S. (1990). Molecular cloning and functional expression of glutamate receptor subunit genes. Science *249*, 1033–1037.

Bowie, D., and Mayer, M.L. (1995). Inward rectification of both AMPA and kainate subtype glutamate receptors generated by polyamine-mediated ion channel block. Neuron *15*, 453–462.

Bowie, D., Lange, G.D., and Mayer, M.L. (1998). Activity-dependent modulation of glutamate receptors by polyamines. J. Neurosci. *18*, 8175–8185.

Brorson, J.R., Li, D., and Suzuki, T. (2004). Selective expression of heteromeric AMPA receptors driven by flip-flop differences. J. Neurosci. *24*, 3461–3470.

Brusa, R., Zimmermann, F., Koh, D.S., Feldmeyer, D., Gass, P., Seeburg, P.H., and Sprengel, R. (1995). Early-onset epilepsy and postnatal lethality associated with an editing-deficient GluR-B allele in mice. Science *270*, 1677–1680.

Carroll, R.C., Beattie, E.C., Xia, H., Luscher, C., Altschuler, Y., Nicoll, R.A., Malenka, R.C., and von Zastrow, M. (1999). Dynamin-dependent endocytosis of ionotropic glutamate receptors. Proc. Natl. Acad. Sci. USA *96*, 14112–14117.

Carroll, R.C., Beattie, E.C., von Zastrow, M., and Malenka, R.C. (2001). Role of AMPA receptor endocytosis in synaptic plasticity. Nat. Rev. Neurosci. *2*, 315–324.

Carter, A.G., and Regehr, W.G. (2002). Quantal events shape cerebellar interneuron firing. Nat. Neurosci. *5*, 1309–1318.

Chen, L., Chetkovich, D.M., Petralia, R.S., Sweeney, N.T., Kawasaki, Y., Wenthold, R.J., Bredt, D.S., and Nicoll, R.A. (2000). Stargazin regulates synaptic targeting of AMPA receptors by two distinct mechanisms. Nature *408*, 936–943.

Chowdhury, S., Shepherd, J.D., Okuno, H., Lyford, G., Petralia, R.S., Plath, N., Kuhl, D., Huganir, R.L., and Worley, P.F. (2006). Arc/Arg3.1 interacts with the endocytic machinery to regulate AMPA receptor trafficking. Neuron *52*, 445–459.

Chung, H.J., Xia, J., Scannevin, R.H., Zhang, X., and Huganir, R.L. (2000). Phosphorylation of the AMPA receptor subunit GluR2 differentially regulates its interaction with PDZ domain-containing proteins. J. Neurosci. *20*, 7258–7267.

Chung, H.J., Steinberg, J.P., Huganir, R.L., and Linden, D.J. (2003). Requirement of AMPA receptor GluR2 phosphorylation for cerebellar long-term depression. Science *300*, 1751–1755.

Clem, R.L., and Barth, A. (2006). Pathway-specific trafficking of native AMPARs by in vivo experience. Neuron *49*, 663–670.

Collingridge, G.L., Isaac, J.T., and Wang, Y.T. (2004). Receptor trafficking and synaptic plasticity. Nat. Rev. Neurosci. *5*, 952–962.

Craig, A.M., Blackstone, C.D., Huganir, R.L., and Banker, G. (1993). The distribution of glutamate receptors in cultured rat hippocampal neurons: postsynaptic clustering of AMPA-selective subunits. Neuron *10*, 1055–1068.

Cull-Candy, S., Kelly, L., and Farrant, M. (2006). Regulation of Ca2+-permeable AMPA receptors: synaptic plasticity and beyond. Curr. Opin. Neurobiol. *16*, 288–297.

Daw, M.I., Chittajallu, R., Bortolotto, Z.A., Dev, K.K., Duprat, F., Henley, J.M., Collingridge, G.L., and Isaac, J.T. (2000). PDZ proteins interacting with C-terminal GluR2/3 are involved in a PKC-dependent regulation of AMPA receptors at hippocampal synapses. Neuron *28*, 873–886.

Desai, N.S., Cudmore, R.H., Nelson, S.B., and Turrigiano, G.G. (2002). Critical periods for experience-dependent synaptic scaling in visual cortex. Nat. Neurosci. *5*, 783–789.

Dev, K.K., Nishimune, A., Henley, J.M., and Nakanishi, S. (1999). The protein kinase C alpha binding protein PICK1 interacts with short but not long form alternative splice variants of AMPA receptor subunits. Neuropharmacology *38*, 635–644.

Dingledine, R., Borges, K., Bowie, D., and Traynelis, S.F. (1999). The glutamate receptor ion channels. Pharmacol. Rev. *51*, 7–61.

Dingledine, R., and Laezza, F. (2004). Voltage controlled plasticity at GluR2-deficient synapses onto hippocampal interneurons. J. Neurophysiol. *92*, 3575–3581.

Dong, H., O'Brien, R.J., Fung, E.T., Lanahan, A.A., Worley, P.F., and Huganir, R.L. (1997). GRIP: a synaptic PDZ domain-containing protein that interacts with AMPA receptors. Nature *386*, 279–284.

Feldmeyer, D., Kask, K., Brusa, R., Kornau, H.C., Kolhekar, R., Rozov, A., Burnashev, N., Jensen, V., Hvalby, O., Sprengel, R., and Seeburg, P.H. (1999). Neurological dysfunctions in mice expressing different levels of the Q/R site-unedited AMPAR subunit GluR-B. Nat. Neurosci. *2*, 57–64.

Frey, U., and Morris, R.G. (1997). Synaptic tagging and long-term potentiation. Nature *385*, 533–536.

Frey, U., and Morris, R.G. (1998). Synaptic tagging: implications for late maintenance of hippocampal long-term potentiation. Trends Neurosci. *21*, 181–188.

Fu, J., deSouza, S., and Ziff, E.B. (2003). Intracellular membrane targeting and suppression of Ser880 phosphorylation of glutamate receptor 2 by the linker I-set II domain of AMPA receptor-binding protein. J. Neurosci. *23*, 7592–7601.

Gardner, S.M., Takamiya, K., Xia, J., Suh, J.G., Johnson, R., Yu, S., and Huganir, R.L. (2005). Calcium-permeable AMPA receptor plasticity is mediated by subunit-specific interactions with PICK1 and NSF. Neuron *45*, 903–915.

Geiger, J.R., Melcher, T., Koh, D.S., Sakmann, B., Seeburg, P.H., Jonas, P., and Monyer, H. (1995). Relative abundance of subunit mRNAs determines gating and Ca2+ permeability of AMPA receptors in principal neurons and interneurons in rat CNS. Neuron *15*, 193–204.

Geiger, J.R., Lubke, J., Roth, A., Frotscher, M., and Jonas, P. (1997). Submillisecond AMPA receptor-mediated signaling at a principal neuron-interneuron synapse. Neuron *18*, 1009–1023.

Gerlai, R., Henderson, J.T., Roder, J.C., and Jia, Z. (1998). Multiple behavioral anomalies in GluR2 mutant mice exhibiting enhanced LTP. Behav. Brain Res. *95*, 37–45.

Goel, A., Jiang, B., Xu, L.W., Song, L., Kirkwood, A., and Lee, H.K. (2006). Cross-modal regulation of synaptic AMPA receptors in primary sensory cortices by visual experience. Nat. Neurosci. *9*, 1001–1003.

Greger, I.H., Khatri, L., and Ziff, E.B. (2002). RNA editing at arg607 controls AMPA receptor exit from the endoplasmic reticulum. Neuron *34*, 759–772.

Greger, I.H., Khatri, L., Kong, X., and Ziff, E.B. (2003). AMPA receptor tetramerization is mediated by Q/R editing. Neuron *40*, 763–774.

Greger, I.H., Akamine, P., Khatri, L., and Ziff, E.B. (2006). Developmentally regulated, combinatorial RNA processing modulates AMPA receptor biogenesis. Neuron *51*, 85–97.

Hanley, J.G., Khatri, L., Hanson, P.I., and Ziff, E.B. (2002). NSF ATPase and alpha-/beta-SNAPs disassemble the AMPA receptor-PICK1 complex. Neuron *34*, 53–67.

Hartmann, B., Ahmadi, S., Heppenstall, P.A., Lewin, G.R., Schott, C., Borchardt, T., Seeburg, P.H., Zeilhofer, H.U., Sprengel, R., and Kuner, R. (2004). The AMPA receptor subunits GluR-A and GluR-B reciprocally modulate spinal synaptic plasticity and inflammatory pain. Neuron *44*, 637–650.

Hayashi, T., and Huganir, R.L. (2004). Tyrosine phosphorylation and regulation of the AMPA receptor by SRC family tyrosine kinases. J. Neurosci. *24*, 6152–6160.

Hayashi, Y., Hattori, Y., Moriwaki, A., Lu, Y.F., and Hori, Y. (1993). Increases in brain polyamine concentrations in chemical kindling and single convulsion induced by pentylenetetrazol in rats. Neurosci. Lett. *149*, 63–66.

Hayashi, Y., Shi, S.H., Esteban, J.A., Piccini, A., Poncer, J.C., and Malinow, R. (2000). Driving AMPA receptors into synapses by LTP and CaMKII: requirement for GluR1 and PDZ domain interaction. Science *287*, 2262–2267.

Herlitze, S., Raditsch, M., Ruppersberg, J.P., Jahn, W., Monyer, H., Schoepfer, R., and Witzemann, V. (1993). Argiotoxin detects molecular differences in AMPA receptor channels. Neuron *10*, 1131–1140.

Hestrin, S. (1993). Different glutamate receptor channels mediate fast excitatory synaptic currents in inhibitory and excitatory cortical neurons. Neuron *11*, 1083–1091.

Higuchi, M., Single, F.N., Kohler, M., Sommer, B., Sprengel, R., and Seeburg, P.H. (1993). RNA editing of AMPA receptor subunit GluR-B: a base-paired intron-exon structure determines position and efficiency. Cell *75*, 1361–1370.

Higuchi, M., Maas, S., Single, F.N., Hartner, J., Rozov, A., Burnashev, N., Feldmeyer, D., Sprengel, R., and Seeburg, P.H. (2000). Point mutation in an AMPA receptor gene rescues lethality in mice deficient in the RNA-editing enzyme ADAR2. Nature *406*, 78–81.

Jia, Z., Agopyan, N., Miu, P., Xiong, Z., Henderson, J., Gerlai, R., Taverna, F.A., Velumian, A., MacDonald, J., Carlen, P., et al. (1996). Enhanced LTP in mice deficient in the AMPA receptor GluR2. Neuron *17*, 945–956.

Jonas, P., and Burnashev, N. (1995). Molecular mechanisms controlling calcium entry through AMPA-type glutamate receptor channels. Neuron *15*, 987–990.

Jonas, P., Racca, C., Sakmann, B., Seeburg, P.H., and Monyer, H. (1994). Differences in Ca2+ permeability of AMPA-type glutamate receptor channels in neocortical neurons caused by differential GluR-B subunit expression. Neuron *12*, 1281–1289.

Jonas, P., Bischofberger, J., Fricker, D., and Miles, R. (2004). Interneuron Diversity series: Fast in, fast out–temporal and spatial signal processing in hippocampal interneurons. Trends Neurosci. *27*, 30–40.

Ju, W., Morishita, W., Tsui, J., Gaietta, G., Deerinck, T.J., Adams, S.R., Garner, C.C., Tsien, R.Y., Ellisman, M.H., and Malenka, R.C. (2004). Activity-dependent regulation of dendritic synthesis and trafficking of AMPA receptors. Nat. Neurosci. *7*, 244–253.

Kamboj, S.K., Swanson, G.T., and Cull-Candy, S.G. (1995). Intracellular spermine confers rectification on rat calcium-permeable AMPA and kainate receptors. J. Physiol. *486*, 297–303.

Kastning, K., Kukhtina, V., Kittler, J.T., Chen, G., Pechstein, A., Enders, S., Lee, S.H., Sheng, M., Yan, Z., and Haucke, V. (2007). Molecular determinants for the interaction between AMPA receptors and the clathrin adaptor complex AP-2. Proc. Natl. Acad. Sci. USA. *104*, 2991–2996.

Kauer, J.A., Malenka, R.C., and Nicoll, R.A. (1988). A persistent postsynaptic modification mediates long-term potentiation in the hippocampus. Neuron *1*, 911–917.

Kim, C.H., Chung, H.J., Lee, H.K., and Huganir, R.L. (2001). Interaction of the AMPA receptor subunit GluR2/3 with PDZ domains regulates hippocampal long-term depression. Proc. Natl. Acad. Sci. USA *98*, 11725–11730.

Koh, D.S., Burnashev, N., and Jonas, P. (1995a). Block of native Ca(2+)-permeable AMPA receptors in rat brain by intracellular polyamines generates double rectification. J. Physiol. *486*, 305–312.

Koh, D.S., Geiger, J.R., Jonas, P., and Sakmann, B. (1995b). Ca(2+)-permeable AMPA and NMDA receptor channels in basket cells of rat hippocampal dentate gyrus. J. Physiol. *485*, 383–402.

Kumar, S.S., Bacci, A., Kharazia, V., and Huguenard, J.R. (2002). A developmental switch of AMPA receptor subunits in neocortical pyramidal neurons. J. Neurosci. *22*, 3005–3015.

Laezza, F., Doherty, J.J., and Dingledine, R. (1999). Long-term depression in hippocampal interneurons: joint requirement for pre- and postsynaptic events. Science *285*, 1411–1414.

Lambolez, B., Ropert, N., Perrais, D., Rossier, J., and Hestrin, S. (1996). Correlation between kinetics and RNA splicing of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors in neocortical neurons. Proc. Natl. Acad. Sci. USA *93*, 1797–1802.

Lamsa, K.P., Heeroma, J.H., Somogyi, P., Rusakov, D.A., and Kullmann, D.M. (2007). Anti-Hebbian long-term potentiation in the hippocampal feedback inhibitory circuit. Science *315*, 1262–1266.

Lapointe, V., Morin, F., Ratte, S., Croce, A., Conquet, F., and Lacaille, J.C. (2004). Synapse-specific mGluR1-dependent long-term potentiation in interneurones regulates mouse hippocampal inhibition. J. Physiol. *555*, 125–135.

Lawrence, J.J., and McBain, C.J. (2003). Interneuron diversity series: Containing the detonation–feedforward inhibition in the CA3 hippocampus. Trends Neurosci. *26*, 631–640.

Lawrence, J.J., Grinspan, Z.M., and McBain, C.J. (2004). Quantal transmission at mossy fibre targets in the CA3 region of the rat hippocampus. J Physiol. *554*, 175–193.

Lee, S.H., Liu, L., Wang, Y.T., and Sheng, M. (2002). Clathrin adaptor AP2 and NSF interact with overlapping sites of GluR2 and play distinct roles in AMPA receptor trafficking and hippocampal LTD. Neuron *36*, 661–674.

Lei, S., and McBain, C.J. (2002). Distinct NMDA receptors provide differential modes of transmission at mossy fiber-interneuron synapses. Neuron *33*, 921–933.

Li, P., Kerchner, G.A., Sala, C., Wei, F., Huettner, J.E., Sheng, M., and Zhuo, M. (1999). AMPA receptor-PDZ interactions in facilitation of spinal sensory synapses. Nat. Neurosci. *2*, 972–977.

Liu, S.J., and Cull-Candy, S.G. (2002). Activity-dependent change in AMPA receptor properties in cerebellar stellate cells. J. Neurosci. *22*, 3881–3889.

Liu, S.J., and Cull-Candy, S.G. (2005). Subunit interaction with PICK and GRIP controls Ca(2+) permeability of AMPARs at cerebellar synapses. Nat. Neurosci. *8*, 768–775.

Liu, S.Q., and Cull-Candy, S.G. (2000). Synaptic activity at calcium-permeable AMPA receptors induces a switch in receptor subtype. Nature *405*, 454–458.

Luscher, C., Xia, H., Beattie, E.C., Carroll, R.C., von Zastrow, M., Malenka, R.C., and Nicoll, R.A. (1999). Role of AMPA receptor cycling in synaptic transmission and plasticity. Neuron *24*, 649–658.

Luthi, A., Chittajallu, R., Duprat, F., Palmer, M.J., Benke, T.A., Kidd, F.L., Henley, J.M., Isaac, J.T., and Collingridge, G.L. (1999). Hippocampal LTD expression involves a pool of AMPARs regulated by the NSF-GluR2 interaction. Neuron *24*, 389–399.

Mahanty, N.K., and Sah, P. (1998). Calcium-permeable AMPA receptors mediate long-term potentiation in interneurons in the amygdala. Nature *394*, 683–687.

Malinow, R., and Malenka, R.C. (2002). AMPA receptor trafficking and synaptic plasticity. Annu. Rev. Neurosci. *25*, 103–126.

Mansour, M., Nagarajan, N., Nehring, R.B., Clements, J.D., and Rosenmund, C. (2001). Heteromeric AMPA receptors assemble with a preferred subunit stoichiometry and spatial arrangement. Neuron *32*, 841–853.

Matsuda, S., Mikawa, S., and Hirai, H. (1999). Phosphorylation of serine-880 in GluR2 by protein kinase C prevents its C terminus from binding with glutamate receptor-interacting protein. J. Neurochem. *73*, 1765–1768.

Matsuda, S., Launey, T., Mikawa, S., and Hirai, H. (2000). Disruption of AMPA receptor GluR2 clusters following long-term depression induction in cerebellar Purkinje neurons. EMBO J. *19*, 2765–2774.

Mayer, M.L. (2006). Glutamate receptors at atomic resolution. Nature *440*, 456–462.

McBain, C.J., and Dingledine, R. (1993). Heterogeneity of synaptic glutamate receptors on CA3 stratum radiatum interneurones of rat hippocampus. J. Physiol. *462*, 373–392.

McBain, C.J., and Fisahn, A. (2001). Interneurons unbound. Nat. Rev. Neurosci. *2*, 11–23.

Meng, Y., Zhang, Y., and Jia, Z. (2003). Synaptic transmission and plasticity in the absence of AMPA glutamate receptor GluR2 and GluR3. Neuron *39*, 163–176.

Monyer, H., Seeburg, P.H., and Wisden, W. (1991). Glutamate-operated channels: developmentally early and mature forms arise by alternative splicing. Neuron *6*, 799–810.

Muller, D., Joly, M., and Lynch, G. (1988). Contributions of quisqualate and NMDA receptors to the induction and expression of LTP. Science *242*, 1694–1697.

Nicoll, R.A., Tomita, S., and Bredt, D.S. (2006). Auxiliary subunits assist AMPA-type glutamate receptors. Science *311*, 1253–1256.

Nishimune, A., Isaac, J.T., Molnar, E., Noel, J., Nash, S.R., Tagaya, M., Collingridge, G.L., Nakanishi, S., and Henley, J.M. (1998). NSF binding to GluR2 regulates synaptic transmission. Neuron *21*, 87–97.

Noel, J., Ralph, G.S., Pickard, L., Williams, J., Molnar, E., Uney, J.B., Collingridge, G.L., and Henley, J.M. (1999). Surface expression of AMPA receptors in hippocampal neurons is regulated by an NSF-dependent mechanism. Neuron *23*, 365–376.

Osten, P., Srivastava, S., Inman, G.J., Vilim, F.S., Khatri, L., Lee, L.M., States, B.A., Einheber, S., Milner, T.A., Hanson, P.I., and Ziff, E.B. (1998). The AMPA receptor GluR2 C terminus can mediate a reversible, ATP-dependent interaction with NSF and alpha- and beta-SNAPs. Neuron *21*, 99–110.

Palmer, C.L., Lim, W., Hastie, P.G., Toward, M., Korolchuk, V.I., Burbidge, S.A., Banting, G., Collingridge, G.L., Isaac, J.T., and Henley, J.M. (2005). Hippocalcin functions as a calcium sensor in hippocampal LTD. Neuron *47*, 487–494.

Passafaro, M., Nakagawa, T., Sala, C., and Sheng, M. (2003). Induction of dendritic spines by an extracellular domain of AMPA receptor subunit GluR2. Nature *424*, 677–681.

Pelkey, K.A., Lavezzari, G., Racca, C., Roche, K.W., and McBain, C.J. (2005). mGluR7 is a metaplastic switch controlling bidirectional plasticity of feedforward inhibition. Neuron *46*, 89–102.

Perez, J.L., Khatri, L., Chang, C., Srivastava, S., Osten, P., and Ziff, E.B. (2001a). PICK1 targets activated protein kinase C alpha to AMPA receptor clusters in spines of hippocampal neurons and reduces surface levels of the AMPA-type glutamate receptor subunit 2. J. Neurosci. *21*, 5417–5428.

Perez, Y., Morin, F., and Lacaille, J.C. (2001b). A hebbian form of long-term potentiation dependent on mGluR1a in hippocampal inhibitory interneurons. Proc. Natl. Acad. Sci. USA *98*, 9401–9406.

Pickard, L., Noel, J., Henley, J.M., Collingridge, G.L., and Molnar, E. (2000). Developmental changes in synaptic AMPA and NMDA receptor distribution and AMPA receptor subunit composition in living hippocampal neurons. J. Neurosci. *20*, 7922–7931.

Plant, K., Pelkey, K.A., Bortolotto, Z.A., Morita, D., Terashima, A., McBain, C.J., Collingridge, G.L., and Isaac, J.T. (2006). Transient incorporation of native GluR2-lacking AMPA receptors during hippocampal long-term potentiation. Nat. Neurosci. *9*, 602–604.

Rial Verde, E.M., Lee-Osbourne, J., Worley, P.F., Malinow, R., and Cline, H.T. (2006). Increased expression of the immediate-early gene arc/arg3.1 reduces AMPA receptor-mediated synaptic transmission. Neuron *52*, 461–474.

Rosenmund, C., Stern-Bach, Y., and Stevens, C.F. (1998). The tetrameric structure of a glutamate receptor channel. Science *280*, 1596–1599.

Rothman, J.E. (1994). Intracellular membrane fusion. Adv. Second Messenger Phosphoprotein Res. *29*, 81–96.

Rouach, N., Byrd, K., Petralia, R.S., Elias, G.M., Adesnik, H., Tomita, S., Karimzadegan, S., Kealey, C., Bredt, D.S., and Nicoll, R.A. (2005). TARP gamma-8 controls hippocampal AMPA receptor number, distribution and synaptic plasticity. Nat. Neurosci. *8*, 1525–1533.

Rozov, A., and Burnashev, N. (1999). Polyamine-dependent facilitation of postsynaptic AMPA receptors counteracts paired-pulse depression. Nature *401*, 594–598.

Rozov, A., Zilberter, Y., Wollmuth, L.P., and Burnashev, N. (1998). Facilitation of currents through rat Ca2+-permeable AMPA receptor channels by activity-dependent relief from polyamine block. J. Physiol. *511*, 361–377.

Saglietti, L., Dequidt, C., Kamieniarz, K., Rousset, M.C., Valnegri, P., Thoumine, O., Beretta, F., Fagni, L., Choquet, D., Sala, C., et al. (2007). Extracellular Interactions between GluR2 and N-Cadherin in Spine Regulation. Neuron *54*, 461–477.

Sans, N., Vissel, B., Petralia, R.S., Wang, Y.X., Chang, K., Royle, G.A., Wang, C.Y., O'Gorman, S., Heinemann, S.F., and Wenthold, R.J. (2003). Aberrant formation of glutamate receptor complexes in hippocampal neurons of mice lacking the GluR2 AMPA receptor subunit. J. Neurosci. *23*, 9367–9373.

Seidenman, K.J., Steinberg, J.P., Huganir, R., and Malinow, R. (2003). Glutamate receptor subunit 2 Serine 880 phosphorylation modulates synaptic transmission and mediates plasticity in CA1 pyramidal cells. J. Neurosci. *23*, 9220–9228.

Sheng, M., and Sala, C. (2001). PDZ domains and the organization of supramolecular complexes. Annu. Rev. Neurosci. *24*, 1–29.

Shepherd, J.D., Rumbaugh, G., Wu, J., Chowdhury, S., Plath, N., Kuhl, D., Huganir, R.L., and Worley, P.F. (2006). Arc/Arg3.1 mediates homeostatic synaptic scaling of AMPA receptors. Neuron *52*, 475–484.

Shi, S., Hayashi, Y., Esteban, J.A., and Malinow, R. (2001). Subunit-specific rules governing AMPA receptor trafficking to synapses in hippocampal pyramidal neurons. Cell *105*, 331–343.

Shimshek, D.R., Bus, T., Grinevich, V., Single, F.N., Mack, V., Sprengel, R., Spergel, D.J., and Seeburg, P.H. (2006a). Impaired reproductive behavior by lack of GluR-B containing AMPA receptors but not of NMDA receptors in hypothalamic and septal neurons. Mol. Endocrinol. *20*, 219–231.

Shimshek, D.R., Jensen, V., Celikel, T., Geng, Y., Schupp, B., Bus, T., Mack, V., Marx, V., Hvalby, O., Seeburg, P.H., and Sprengel, R. (2006b). Forebrain-specific Glutamate Receptor B deletion impairs spatial memory but not hippocampal field long-term potentiation. J. Neurosci. *26*, 8428–8440.

Shin, J., Shen, F., and Huguenard, J.R. (2005). Polyamines modulate AMPA receptor-dependent synaptic responses in immature layer V pyramidal neurons. J. Neurophysiol. *93*, 2634–2643.

Sommer, B., Kohler, M., Sprengel, R., and Seeburg, P.H. (1991). RNA editing in brain controls a determinant of ion flow in glutamate-gated channels. Cell *67*, 11–19.

Song, I., Kamboj, S., Xia, J., Dong, H., Liao, D., and Huganir, R.L. (1998). Interaction of the N-ethylmaleimide-sensitive factor with AMPA receptors. Neuron *21*, 393–400.

Sorkin, A. (2004). Cargo recognition during clathrin-mediated endocytosis: a team effort. Curr. Opin. Cell Biol. *16*, 392–399.

Soulet, D., and Rivest, S. (2003). Polyamines play a critical role in the control of the innate immune response in the mouse central nervous system. J. Cell Biol. *162*, 257–268.

Srivastava, S., Osten, P., Vilim, F.S., Khatri, L., Inman, G., States, B., Daly, C., DeSouza, S., Abagyan, R., Valtschanoff, J.G., et al. (1998). Novel anchorage of GluR2/3 to the postsynaptic density by the AMPA receptor-binding protein ABP. Neuron *21*, 581–591.

Steinberg, J.P., Takamiya, K., Shen, Y., Xia, J., Rubio, M.E., Yu, S., Jin, W., Thomas, G.M., Linden, D.J., and Huganir, R.L. (2006). Targeted in vivo mutations of the AMPA receptor subunit GluR2 and its interacting protein PICK1 eliminate cerebellar long-term depression. Neuron *49*, 845–860.

Stellwagen, D., and Malenka, R.C. (2006). Synaptic scaling mediated by glial TNF-alpha. Nature *440*, 1054–1059.

Stellwagen, D., Beattie, E.C., Seo, J.Y., and Malenka, R.C. (2005). Differential regulation of AMPA receptor and GABA receptor trafficking by tumor necrosis factor-alpha. J. Neurosci. *25*, 3219–3228.

Sutton, M.A., Ito, H.T., Cressy, P., Kempf, C., Woo, J.C., and Schuman, E.M. (2006). Miniature neurotransmission stabilizes synaptic function via tonic suppression of local dendritic protein synthesis. Cell *125*, 785–799.

Swanson, G.T., Kamboj, S.K., and Cull-Candy, S.G. (1997). Single-channel properties of recombinant AMPA receptors depend on RNA editing, splice variation, and subunit composition. J. Neurosci. *17*, 58–69.

Tabor, C.W., and Tabor, H. (1984). Polyamines. Annu. Rev. Biochem. *53*, 749–790.

Terashima, A., Cotton, L., Dev, K.K., Meyer, G., Zaman, S., Duprat, F., Henley, J.M., Collingridge, G.L., and Isaac, J.T. (2004). Regulation of synaptic strength and AMPA receptor subunit composition by PICK1. J. Neurosci. *24*, 5381–5390.

Thiagarajan, T.C., Lindskog, M., and Tsien, R.W. (2005). Adaptation to synaptic inactivity in hippocampal neurons. Neuron *47*, 725–737.

Tomita, S., Chen, L., Kawasaki, Y., Petralia, R.S., Wenthold, R.J., Nicoll, R.A., and Bredt, D.S. (2003). Functional studies and distribution define a family of transmembrane AMPA receptor regulatory proteins. J. Cell Biol. *161*, 805–816.

Tomita, S., Adesnik, H., Sekiguchi, M., Zhang, W., Wada, K., Howe, J.R., Nicoll, R.A., and Bredt, D.S. (2005). Stargazin modulates AMPA receptor gating and trafficking by distinct domains. Nature *435*, 1052–1058.

Topolnik, L., Congar, P., and Lacaille, J.C. (2005). Differential regulation of metabotropic glutamate receptor- and AMPA receptor-mediated dendritic Ca2+ signals by presynaptic and postsynaptic activity in hippocampal interneurons. J. Neurosci. *25*, 990–1001.

Toth, K., and McBain, C.J. (1998). Afferent-specific innervation of two distinct AMPA receptor subtypes on single hippocampal interneurons. Nat. Neurosci. *1*, 572–578.

Toth, K., Suares, G., Lawrence, J.J., Philips-Tansey, E., and McBain, C.J. (2000). Differential mechanisms of transmission at three types of mossy fiber synapse. J. Neurosci. *20*, 8279–8289.

Tsuzuki, K., Lambolez, B., Rossier, J., and Ozawa, S. (2001). Absolute quantification of AMPA receptor subunit mRNAs in single hippocampal neurons. J. Neurochem. *77*, 1650–1659.

Turrigiano, G.G., and Nelson, S.B. (2004). Homeostatic plasticity in the developing nervous system. Nat. Rev. Neurosci. *5*, 97–107.

Turrigiano, G.G., Leslie, K.R., Desai, N.S., Rutherford, L.C., and Nelson, S.B. (1998). Activity-dependent scaling of quantal amplitude in neocortical neurons. Nature *391*, 892–896.

Tzingounis, A.V., and Nicoll, R.A. (2006). Arc/Arg3.1: linking gene expression to synaptic plasticity and memory. Neuron *52*, 403–407.

Verdoorn, T.A., Burnashev, N., Monyer, H., Seeburg, P.H., and Sakmann, B. (1991). Structural determinants of ion flow through recombinant glutamate receptor channels. Science *252*, 1715–1718.

Vida, I., Bartos, M., and Jonas, P. (2006). Shunting inhibition improves robustness of gamma oscillations in hippocampal interneuron networks by homogenizing firing rates. Neuron *49*, 107–117.

Walker, H.C., Lawrence, J.J., and McBain, C.J. (2002). Activation of kinetically distinct synaptic conductances on inhibitory interneurons by electrotonically overlapping afferents. Neuron *35*, 161–171.

Washburn, M.S., and Dingledine, R. (1996). Block of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors by polyamines and polyamine toxins. J. Pharmacol. Exp. Ther. *278*, 669–678.

Washburn, M.S., Numberger, M., Zhang, S., and Dingledine, R. (1997). Differential dependence on GluR2 expression of three characteristic features of AMPA receptors. J. Neurosci. *17*, 9393–9406.

Watanabe, S., Kusama-Eguchi, K., Kobayashi, H., and Igarashi, K. (1991). Estimation of polyamine binding to macromolecules and ATP in bovine lymphocytes and rat liver. J. Biol. Chem. *266*, 20803–20809.

Watt, A.J., van Rossum, M.C., MacLeod, K.M., Nelson, S.B., and Turrigiano, G.G. (2000). Activity coregulates quantal AMPA and NMDA currents at neocortical synapses. Neuron *26*, 659–670.

Wenthold, R.J., Petralia, R.S., Blahos, J., II, and Niedzielski, A.S. (1996). Evidence for multiple AMPA receptor complexes in hippocampal CA1/CA2 neurons. J. Neurosci. *16*, 1982–1989.

Wisden, W., and Seeburg, P.H. (1993). Mammalian ionotropic glutamate receptors. Curr. Opin. Neurobiol. *3*, 291–298.

Wu, T.Y., Liu, C.I., and Chang, Y.C. (1996). A study of the oligomeric state of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-preferring glutamate receptors in the synaptic junctions of porcine brain. Biochem. J. *319*, 731–739.

Xia, J., Zhang, X., Staudinger, J., and Huganir, R.L. (1999). Clustering of AMPA receptors by the synaptic PDZ domain-containing protein PICK1. Neuron *22*, 179–187.

Xia, J., Chung, H.J., Wihler, C., Huganir, R.L., and Linden, D.J. (2000). Cerebellar long-term depression requires PKC-regulated interactions between GluR2/3 and PDZ domain-containing proteins. Neuron *28*, 499–510.

Yan, J., Zhang, Y., Jia, Z., Taverna, F.A., McDonald, R.J., Muller, R.U., and Roder, J.C. (2002). Place-cell impairment in glutamate receptor 2 mutant mice. J. Neurosci. *22*, RC204.

Ziff, E.B. (2007). TARPs and the AMPA receptor trafficking paradox. Neuron *53*, 627–633.

Zoli, M., Zini, I., Grimaldi, R., Biagini, G., and Agnati, L.F. (1993). Effects of polyamine synthesis blockade on neuronal loss and astroglial reaction after transient forebrain ischemia. Int. J. Dev. Neurosci. *11*, 175–187.