Neuron
Perspective

AMPARs and Synaptic Plasticity: The Last 25 Years

Richard L. Huganir[1,*] and Roger A. Nicoll[2,*]
[1]Solomon H. Snyder Department of Neuroscience, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
[2]Departments of Cellular and Molecular Pharmacology, University of California San Francisco, San Francisco, CA 94143, USA
*Correspondence: rhuganir@jhmi.edu (R.L.H.), roger.nicoll@ucsf.edu (R.A.N.)
http://dx.doi.org/10.1016/j.neuron.2013.10.025

The study of synaptic plasticity and specifically LTP and LTD is one of the most active areas of research in neuroscience. In the last 25 years we have come a long way in our understanding of the mechanisms underlying synaptic plasticity. In 1988, AMPA and NMDA receptors were not even molecularly identified and we only had a simple model of the minimal requirements for the induction of plasticity. It is now clear that the modulation of the AMPA receptor function and membrane trafficking is critical for many forms of synaptic plasticity and a large number of proteins have been identified that regulate this complex process. Here we review the progress over the last two and a half decades and discuss the future challenges in the field.

It is a pleasure to join in celebrating the 25th anniversary of *Neuron*. Happy birthday! Our goal is to review the major milestones in the field of synaptic plasticity during the past 25 years, with an emphasis on AMPA receptors (AMPARs) and long-term potentiation (LTP). When viewed up close, science, and in particular LTP, appears to progress at a snail's pace. However, stepping back and viewing the past 25 years it is astounding how much progress has occurred in our understanding of the cellular and molecular underpinnings of synaptic plasticity. In 1988 one of us (R.A.N.) contributed a review entitled "The Current Excitement in Long-Term Potentiation" to Volume 1 of *Neuron* (Nicoll et al., 1988), while the other one (R.L.H) had just started studying the regulation of AMPAR function. Thus, it is relatively easy to compare our knowledge of synaptic plasticity and AMPARs at the launch of *Neuron* to our current understanding. We have come a long way. For more comprehensive reviews on this topic, the reader is referred to a number of reviews (Bredt and Nicoll, 2003; Collingridge et al., 2004; Lüscher and Malenka, 2012; Malinow and Malenka, 2002; Shepherd and Huganir, 2007).

Setting the Stage

When LTP was discovered at dentate granule neuron excitatory synapses (Bliss and Lomo, 1973; Lomo, 1966), the transmitter released from these and other excitatory synapses had not been firmly established. A rich pharmacology of glutamate receptors followed soon after and it became clear that glutamate, acting on NMDA receptors (NMDARs) and non-NMDARs (later referred to as AMPARs and kainate receptors), was the transmitter released from most excitatory synapses. The mid-1980s, as *Neuron* was being conceived, saw a remarkable series of discoveries addressing the initial steps in the induction of LTP. These included the following: the requirement of NMDAR activation (Collingridge et al., 1983), the requirement of a rise in postsynaptic calcium (Lynch et al., 1983), the requirement of postsynaptic depolarization (Malinow and Miller, 1986; Wigström et al., 1986), and the finding that NMDARs exhibit a voltage-dependent block by magnesium (Mayer et al., 1984; Nowak et al., 1984) and are permeable to calcium (Ascher and Nowak, 1988; Jahr and Stevens, 1987). As *Neuron* was launched a model for the induction of LTP, which remains unaltered to this day, was born. In brief, binding of glutamate to NMDARs coupled with depolarization of the postsynaptic membrane, which relieves the magnesium channel block, results in the entry of calcium through the NMDAR and a rise in spine calcium (Figure 1) (Nicoll et al., 1988). Around this time, Ito et al. (1982) reported that pairing cerebellar climbing fiber stimulation with parallel fiber stimulation caused a long-term depression (LTD) of parallel fiber responses as well as to the responses to iontophoretically delivered glutamate. Ten years later NMDAR-dependent LTD was discovered in the hippocampus (Dudek and Bear, 1992). Hippocampal LTP and LTD and cerebellar LTD are arguably the most studied forms of synaptic plasticity and are the primary focus of this review.

Long-Term Potentiation: The Last 25 Years

Much of the first half of this period was consumed by the debate over whether LTP expression is due to an increase in glutamate release or an increase in the postsynaptic sensitivity to glutamate (Bliss and Collingridge, 2013; Bredt and Nicoll, 2003; Nicoll and Roche, 2013). The discovery of silent synapses and their unsilencing during LTP (Isaac et al., 1995; Liao et al., 1995) provided a postsynaptic explanation for the decrease in synaptic failure rate during LTP, the strongest evidence for a presynaptic expression mechanism. This turned the tide of public opinion to a postsynaptic expression mechanism. Perhaps the most definitive demonstration of a postsynaptic expression mechanism comes from glutamate uncaging experiments (Harvey and Svoboda, 2007; Matsuzaki et al., 2004), in which repetitive activation of NMDARs on a single spine results in a long-lasting increase in the uncaging AMPAR response from the same spine. In addition to the increase in AMPAR responses the spine volume increases and follows the same time course as the enhancement in the AMPAR response. Interestingly, most manipulations that block structural plasticity also block LTP. Thus, structural plasticity has often been used as a proxy for LTP. These findings do not exclude an additional presynaptic mechanism, but since the magnitude of the enhancement found in the uncaging experiments is similar to those found with pairing synaptic stimulation with postsynaptic depolarization, there is no need to invoke a presynaptic component, at least during the first hour, the time window most studied.

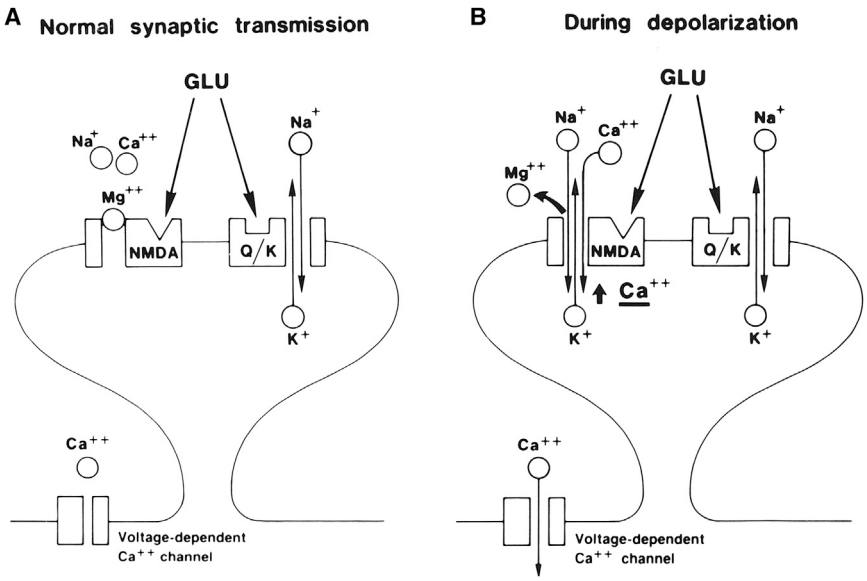

Figure 1. Model Published in 1988 for the Mechanism of Induction of LTP in the CA1 Region of the Hippocampus

(A) The events occurring during low-frequency synaptic transmission. Glutamate is released from the presynaptic terminal and acts on both the NMDA and the Q/K type of receptors (now called AMPA Receptors). Na^+ and K^+ flow through the Q/K receptor channel, but not through the NMDA receptor channel, due to Mg^{+2} block of this channel.

(B) The events occurring when the postsynaptic membrane is depolarized, as would occur during a high-frequency tetanus. The depolarization relieves the Mg^{+2} block of the NMDA channel, allowing Na^+, K^+, and most importantly Ca^{+2} to flow through the channel. The rise in Ca^{+2} in the dendritic spines is proposed to provide a trigger for subsequent events leading to LTP. Depolarization would also open voltage-dependent Ca^{+2} channels on the dendritic shafts, but this source of Ca^{+2} does not have access to the spine. It is important to note that this model includes only events involved in the induction of LTP and not in its maintenance (taken from Nicoll et al., 1988).

Much of the research on LTP during the past decade has focused on the role of CaMKII in LTP (Lisman et al., 2012) and AMPAR trafficking (Anggono and Huganir, 2012; Kessels and Malinow, 2009; Lüscher and Malenka, 2012; Nicoll and Roche, 2013). Considerable evidence indicates that CaMKII is the primary downstream target following calcium entry through the NMDAR and is both necessary and sufficient for LTP. Two interesting areas of research concern the activity-dependent translocation of CaMKII to the synapse and the role of CaMKII as a memory molecule. Elevated calcium in the spine recruits CaMKII to the PSD. This involves the activity-dependent binding of CaMKII to the GluN2B subunit of the NMDAR, thus ideally positioning it for optimal activation by calcium and the phosphorylation of PSD proteins. Disrupting this binding impairs LTP (Barria and Malinow, 2005; Halt et al., 2012; Zhou et al., 2007). A long-held model is that the autophosphorylation of CaMKII converts it to a calcium-independent constitutively active enzyme and thus makes it ideally suited to be a "memory molecule" (Lisman et al., 2012). However, recent two-photon fluorescence lifetime imaging of the activation of CaMKII in single spines casts doubt on this attractive model. The activation of CaMKII during LTP induction is only transient, returning to baseline within a few minutes (Lee et al., 2009). This finding implies that the persistence of LTP must rely on signaling cascades downstream of CaMKII. In addition to phosphorylating the GluA1 subunit of the AMPAR (Barria et al., 1997; Mammen et al., 1997; Roche et al., 1996), CaMKII also phosphorylates a number of other PSD proteins, such as PSD-95, synGAP, and the GluN2B subunit of the NMDAR (Dosemeci and Jaffe, 2010; Yoshimura et al., 2000, 2002). However, none of these sites appear to fully account for LTP. Recently, it has been shown that CaMKII can trigger the local persistent activation of the Ras and Rho GTPases (RhoA and Cdc42), which are important for both structural and functional plasticity (Murakoshi et al., 2011). The step(s) between CaMKII activation and Ras and Rho GTPase activation remain unclear.

AMPAR Phosphorylation and LTP

Results in the late 1980s indicating that protein kinase activity, and particularly CaMKII activity, was required for the induction of LTP indicated that protein phosphorylation-dephosphorylation may be critical for LTP and LTD and other forms of synaptic plasticity (Malenka et al., 1989; Malinow et al., 1989; Wyllie and Nicoll, 1994). This led to a relatively simple hypothesis that direct phosphorylation of AMPAR subunits may regulate receptor function and potentiate synaptic transmission (Soderling, 1993; Swope et al., 1992). With the cloning of AMPAR subunits (Traynelis et al., 2010) and the generation of subunit-specific antibodies (Blackstone et al., 1992; Molnár et al., 1993) this could be directly examined. AMPARs consist of four homologous major core subunits (GluA1-4) that form heteromeric tetrameric complexes (Traynelis et al., 2010). The major forms of receptors in the hippocampus include GluA1/2 and GluA2/3 heteromers as well as GluA1 homomers (Lu et al., 2009; Wenthold et al., 1996). These subunits were shown to be directly phosphorylated in the mid-1990s (Blackstone et al., 1994; McGlade-McCulloh et al., 1993; Moss et al., 1993; Tan et al., 1994) and it is now known that the GluA1-4 subunits are phosphorylated on serine, threonine, and tyrosine residues by several protein kinases including CaMKII, PKA, PKC, PKG, FYN, and JNK on over 20 different phosphorylation sites (three to five sites per subunit) (Lu and Roche, 2012; Shepherd and Huganir, 2007). A major focus of research has been on the CaMKII, PKA, and PKC sites on GluA1 and the major PKC site on GluA2. These sites have been shown to be regulated by neuronal activity, and by glutamate through NMDAR and metabotropic glutamate receptor activation as well as by many neuromodulators including norepinephrine, dopamine, and serotonin as well as neuropeptides (Lu and Roche, 2012; Shepherd and Huganir, 2007). The finding that CaMKII could directly phosphorylate GluA1 and regulate its function led to the idea that these phosphorylation events could mediate synaptic potentiation during LTP. Intriguingly, previous studies had shown that the single-channel conductance of

AMPARs changes after LTP expression (Benke et al., 1998) and CaMKII phosphorylation of GluA1 is now known to regulate AMPAR channel conductance (Derkach et al., 1999; Kristensen et al., 2011). Further studies in the late 1990s showed that LTP and LTD could bidirectionally regulate phosphorylation of these sites with LTP increasing phosphorylation and LTD decreasing phosphorylation (Barria et al., 1997; Kameyama et al., 1998; Lee et al., 2000, 1998). The strongest evidence for a role of phosphorylation in LTP and LTD expression comes from experiments using knockin mice where the GluA1 CaMKII and PKA sites are mutated so they cannot be phosphorylated (Lee et al., 2003). Significant deficits in LTP and LTD induction were observed in these mice indicating that phosphorylation of GluA1 was critical for LTP and LTD expression. Moreover, these mutant mice had significant deficits in retention of spatial memory (Lee et al., 2003). Further studies since then have indicated that phosphorylation of these sites are not absolutely required for LTP expression but significantly modulate LTP induction. For example, phosphorylation of GluA1 on the PKA site after norepinephrine treatment lowers the threshold for LTP induction and also lowers the threshold of fear conditioning (Hu et al., 2007). Phosphorylation of both the PKA and CaMKII site on GluA1 is also critical for neuromodulator regulation of spike-timing-dependent plasticity in the visual cortex (Seol et al., 2007). Moreover, phosphorylation of serine 831 is required for serotonin-dependent potentiation of excitatory synaptic transmission at the temporoammonic-CA1 synapses in the hippocampus (Cai et al., 2013). Interestingly, knockin mice that have mutations that mimic phosphorylation of the CaMKII and PKA phosphorylation sites have a lower threshold for LTP induction, which occludes the effect of norepinephrine and also lowers the threshold for spike-timing-dependent plasticity (Makino et al., 2011). Finally, studies using a knockin mutant mouse where the PKC phosphorylation of serine 880 on the GluA2 subunit is eliminated abolishes cerebellar LTD (see below).

Dynamic Regulation of AMPAR Membrane Trafficking

The discovery of silent synapses and the regulation of AMPAR responses during LTP and LTD strongly supported a postsynaptic locus for the expression of synaptic plasticity (Isaac et al., 1995; Liao et al., 1995). However, was this increased postsynaptic sensitivity due to the regulation of individual receptor function, such as ion channel conductance and open probability, or could it be due to changes in the number of receptors at synapses? Dogma from the neuromuscular junction suggested that receptors at synapses are very stable with minimal dynamic regulation (Sanes and Lichtman, 1999). However, in the late 1990s it was found that AMPAR membrane trafficking was dynamic and could be modified by long-term and short-term changes in neuronal activity.

Physiological studies using compounds such as botulinum toxin and inhibitors of the NSF protein that regulate membrane trafficking were some of the first studies to suggest that membrane trafficking of receptors was dynamic and that dynamic trafficking was important for the expression of LTP and LTD (Lledo et al., 1998; Lüscher et al., 1999). In addition, immunolabeling of synapses in culture demonstrated that there were ''morphological silent synapses'' that contained NMDA receptors but did not have AMPARs, indicating that synapses could vary in their levels of AMPARs (Gomperts et al., 1998; Liao et al., 2001, 1999; Takumi et al., 1999). Studies in culture first demonstrated directly the dynamic rapid trafficking of AMPARs. Treatment of cultures with glutamate or NMDA, a method to chemically induce LTD (Kameyama et al., 1998), resulted in the rapid endocytosis of AMPARs (Beattie et al., 2000; Carroll et al., 1999; Ehlers, 2000). Treatment of cultures with AMPA also induced rapid endocytosis. Interestingly, AMPARs could be differentially sorted in endosomal compartments and were in some cases rapidly recycled back into the plasma membrane and sometimes targeted to lysosomes for degradation (Figure 2). The differential sorting and recycling of AMPARs is now a major area of research and may have important ramifications on synaptic transmission and plasticity. These results indicate that dynamic rapid trafficking of receptors to and from the synapse could play a critical role in the steady state level of receptors at synapses to regulate synaptic strength. The role of AMPAR membrane trafficking in LTP and LTD was directly visualized in 1999 using GFP-tagged receptors expressed in organotypic hippocampal slices using Sindbis virus (Shi et al., 1999). Using this novel system it was shown that GFP-GluA1 was recruited to synaptic spines after LTP induction and this recruitment paralleled synaptic strengthening (Hayashi et al., 2000; Shi et al., 1999). Additional studies using transfected organotypic hippocampal slices further characterized the delivery of AMPARs during LTP and LTD (see below).

In addition to the dynamic membrane trafficking of AMPAR in and out of the plasma membrane it was also discovered in the early 2000s that receptors are rapidly mobile within the plane of the plasma membrane (Opazo and Choquet, 2011; Opazo et al., 2012). Using single-particle tracking techniques it was found that AMPARs in the extrasynaptic membranes are very mobile and can enter synapses where they decrease their mobility (Borgdorff and Choquet, 2002). Using this technique it was shown that the AMPAR auxiliary subunit stargazin and the synaptic scaffolding protein PSD-95 decrease lateral mobility and play an important role in the immobilization of receptors at synapses (Opazo and Choquet, 2011). These data support the idea that AMPARs traffic in and out of the membrane extrasynaptically and then diffuse in and out of the synapse to regulate the steady state number of synaptic AMPARs. Studies in organotypic hippocampal cultures using FRAP of superecliptic pHluorin-tagged AMPARs suggest that AMPARs are exclusively recruited to synapses by lateral diffusion during LTP (Makino and Malinow, 2009).

In addition to the rapid regulation of synaptic levels of AMPARs, long-term modulation of the activity of neurons with inhibitors (TTX, CNQX, APV) or activators (bicuculline, picrotoxin) also regulates AMPAR responses and AMPAR levels at synapses (Lissin et al., 1998; O'Brien et al., 1998; Turrigiano et al., 1998). This regulation of AMPARs by intrinsic activity, called synaptic scaling, is a homeostatic response to long-term changes in network activity (for review, see Turrigiano [2008]).

Scaffolding and Trafficking Proteins

AMPARs and NMDARs are concentrated at excitatory synapses (Craig et al., 1993) and must interact with the local cytoskeleton

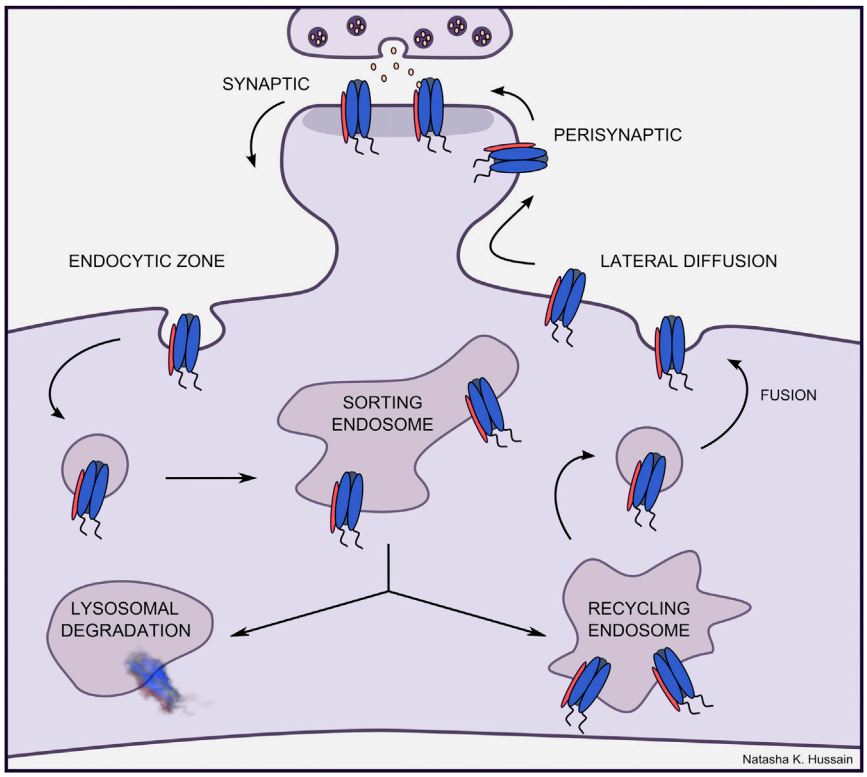

Figure 2. Dynamic AMPAR Trafficking during Synaptic Plasticity

AMPARs are now known to rapidly traffic between membrane compartments and to be highly mobile within the plasma membrane. Receptors rapidly move laterally in the extrasynaptic plasma membrane and can enter and exit synapses where they interact with scaffold proteins within the PSD to immobilize them and concentrate them at the synaptic plasma membrane. The receptors can be endocytosed and then move through endosomal compartments to be sorted for degradation or for recycling back to the plasma membrane. This trafficking is highly regulated during LTP and LTD resulting in increases or decreases in the steady state level of receptors at the synapse. During LTP, receptors from nonsynaptic pools, either from the dendritic shaft plasma membrane or from intracellular pools, are recruited to synapses to potentiate synaptic transmission. In contrast, during LTD, receptors diffuse from the synapse and are then endocytosed and degraded resulting in decreases in synaptic strength.

or synaptic structures such as the postsynaptic density (PSD) to help maintain this local high density. In 1995 it was found that PSD-95 (Kornau et al., 1995), a major component of the PSD (Cho et al., 1992), directly interacted with NMDA receptors (Figure 3). This finding indicated that PSD molecules directly interact with glutamate receptors and potentially modulate the level of receptors at synapses to regulate synaptic strength. PSD-95 was the founding member of a family of synaptic proteins containing modular protein-protein motifs called PDZ domains that serve as scaffolding proteins at synapses (Sheng and Sala, 2001; Xu, 2011). PDZ domains bind to the C-termini of many ion channels, including NMDARs and AMPARs, and are involved in the subcellular targeting of their interacting partners. Many other PDZ domain-containing proteins have been discovered at the synapse including three other proteins highly homologous to PSD-95, PSD-93, SAP102, and SAP97, collectively called MAGUK proteins (Figure 3). Initially these proteins were assumed to be critical for NMDAR synaptic targeting; however, the effects of decreasing the expression of these MAGUKs on NMDARs are quite variable. The MAGUKs, however, appear to be more important for AMPAR targeting to synapses, but they can have overlapping functions (Xu, 2011; Zheng et al., 2011). Early studies showed that overexpression of PSD-95 could increase synapse formation and increase AMPAR levels at synapses (Béïque and Andrade, 2003; El-Husseini et al., 2000). Increasing or decreasing the levels of PSD-95 and PSD-93 increase and decrease synaptic AMPARs, respectively (Béïque et al., 2006; Ehrlich and Malinow, 2004; Elias et al., 2006; Schlüter et al., 2006). Similar manipulations with SAP102 and SAP97 are generally less dramatic and more variable and seem to depend in part on the maturity of the neurons. On a background of reduced PSD-95 expression, SAP97 can fully rescue the deficit in synaptic AMPARs (Howard et al., 2010; Schlüter et al., 2006). Knocking out PSD-95 and SAP-102 genes paradoxically enhances LTP expression (Xu, 2011). In contrast, PSD-95 KO mice have no LTD (Xu et al., 2008). These results suggest a complex relationship between the MAGUK proteins and synaptic plasticity. The role of these scaffolding proteins in the expression and maintenance of LTP is an area of continuing investigation (see below).

In the mid-1990s several labs began to look for AMPAR-interacting proteins that may be involved in their synaptic targeting and membrane trafficking. Using yeast two-hybrid techniques several proteins were found to bind to the C-terminal domains of AMPAR subunits in a subunit-specific manner (Figure 3). GluA2 and GluA3 were found to bind though their C-terminal PDZ ligands to the PDZ domain-containing proteins GRIP1 and 2 (Dong et al., 1997, 1999; Srivastava and Ziff, 1999) and PICK1 (Xia et al., 1999; Dev et al., 2000; Lüscher et al., 1999). In addition, GluA2 was selectively shown to bind to the NSF protein (Nishimune et al., 1998; Osten et al., 1998; Song et al., 1998), a protein critical for regulating membrane trafficking. Disruption of GuA2 binding to PICK1 has been shown to inhibit LTD in both the hippocampus (Kim et al., 2001; Seidenman et al., 2003) and the cerebellum (Chung et al., 2000) while knocking out or knocking down PICK1 has been reported to result in deficits in LTP and LTD in the hippocampus (Citri et al., 2010; Terashima et al., 2008; Volk et al., 2010) and cerebellum (see below). The GluA1 subunit was shown to bind to the PSD-95 family member SAP97 through its C-terminal PDZ domain (Leonard et al., 1998) and also binds to the cytoskeletal protein 4.1N protein through a membrane proximal domain (Lin et al., 2009).

Interestingly, the binding of several of these proteins to AMPAR subunits is regulated by posttranslational modification

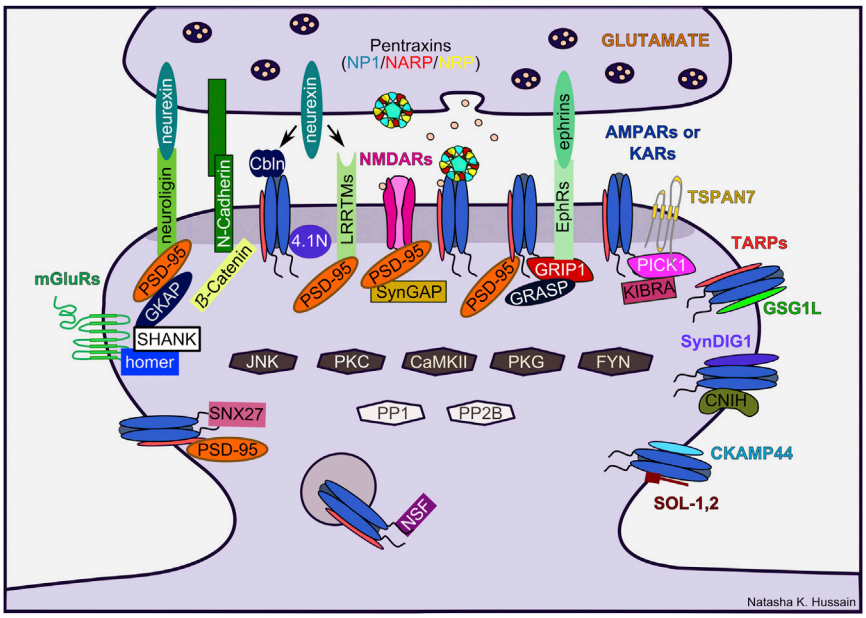

Figure 3. Scaffolding and Trafficking Proteins Involved in AMPAR Membrane Trafficking and Synaptic Plasticity

Over the last 25 years a molecular machine involved in the structure and function of the excitatory synapse and the regulation of AMPAR membrane trafficking has been revealed. Dozens of proteins have been identified including signaling proteins such as protein kinases (PKA, CaMKII, PKC) and phosphatases (PP2B, PP1) that regulate receptor trafficking as well as proteins that directly or indirectly interact with receptors to immobilize them within the PSD. Central to this PSD structural complex are the MAGUKs, PSD-95, PSD-93, SAP97, and SAP102, which interact with many other proteins to modulate the structure and function of the synapse. Additional proteins, such as NSF, GRIP1/2, and PICK, can couple receptors to the endocytic or exocytic machinery to regulate exocytosis or endocytosis or help escort them through endosomal pathways. Recently, several transynaptic proteins such as neuroligins, neurexins, and the LRRTMs have been linked not only to synapse formation but also to AMPAR trafficking and synaptic plasticity. For reviews, see Anggono and Huganir (2012), Sheng and Sala (2001), Shepherd and Huganir (2007), Xu (2011), and Zheng et al. (2011).

and is important for several forms of synaptic plasticity. PKC phosphorylation of GluA2 within its PDZ ligand disrupts binding of GluA2 to GRIP1/2 and increases its binding to PICK1 (Chung et al., 2000; Matsuda et al., 1999). This modulation is required for cerebellar LTD (Steinberg et al., 2006) and may also be important for plasticity in other areas of the brain. The interaction of GluA1 with the 4.1N protein is also regulated by PKC phosphorylation of a membrane proximal region of GluA1 (Lin et al., 2009). Interestingly, PKC phosphorylation of this region is negatively regulated by palmitoylation (Hayashi et al., 2009), indicating a complex interaction between phosphorylation and palmitoylation of GluA1. The 4.1N protein and the PKC phosphorylation sites on GluA1 have been shown to be required for expression of LTP (Boehm et al., 2006; Lin et al., 2009). The interaction of GluA1 with 4.1N regulates the insertion of AMPARs as measured using TIRF microscopy and regulates extrasynaptic reserve pools of AMPARs that may be required for the recruitment of receptors to synapses during LTP (Lin et al., 2009). The requirement for a significant surface pool of receptors for the expression of LTP is a recent recurring theme in current models of LTP (Granger et al., 2013; Nicoll and Roche, 2013; Opazo and Choquet, 2011).

Subunit Dependence of AMPAR Trafficking and LTP and LTD

Although AMPAR subunits are quite homologous in structure, their C-terminal domains are divergent and contain unique phosphorylation sites and interact with distinct proteins. This suggested that they might convey subunit-specific mechanisms for the control of their function and/or membrane trafficking. Indeed there is considerable evidence for subunit dependence of trafficking. In transfected hippocampal organotypic slices the delivery of AMPARs to synapses after LTP induction appears to require GluA1 and its PDZ ligand (Hayashi et al., 2000). In addition, further studies using this system demonstrated that the trafficking of AMPARs is subunit dependent with GluA1/2 heteromers being recruited to spines after LTP, while Glu2/3 heteromers are recruited to synapses in a constitutive manner (Shi et al., 2001). Other evidence suggested that activity-dependent regulation of endocytosis as well as LTD required the GluA2 subunit both in neuronal cell culture and in organotypic hippocampal slices (Lee et al., 2004; Shi et al., 2001). These results indicated that there are subunit-specific roles in LTP and LTD expression with GluA1 being required for LTP and GluA2 being required for LTD.

Although most AMPARs contain the GluA2 subunit and are calcium impermeable, GluA2-lacking and calcium-permeable AMPARs (CP-AMPARs), most likely GluA1 homomers, have been implicated in LTP and other forms of synaptic plasticity. It was reported that after LTP induction GluA1 homomeric CP-AMPARs are initially recruited to synapses followed by GluA2-containing receptors (Plant et al., 2006). Similar observations have been made in cell culture models of LTP (Jaafari et al., 2012), suggesting that there are subunit-specific roles in the expression of LTP. However, this result is highly controversial (Adesnik and Nicoll, 2007) and future studies are needed to understand the role, if any, of CP-AMPARs in hippocampal LTP.

Recent studies (Granger et al., 2013) have called into question whether there is any subunit dependence of basal membrane/synaptic trafficking and the expression of LTP. Molecular replacement approaches, where endogenous AMPAR subunits are knocked out and replaced with different subunits, have shown no specific subunit requirement for LTP and, in fact, exogenously expressed kainate receptors can actually support LTP expression. How might these results be reconciled with the previous literature? In the studies of Granger et al. a pairing induction protocol was used to induce LTP, which generates a near saturating level of LTP. Many of the previous studies used tetanic stimulation, which typically generates lower levels of

potentiation. Thus, while the C-terminal domains are not essential for LTP, it would not be surprising that they would affect the threshold and the magnitude of LTP induced by weaker induction protocols. These findings are making the field re-evaluate the core mechanisms of LTP and have put a spotlight on the scaffolding proteins and transsynaptic membrane proteins as important modulators of plasticity.

AMPAR Auxiliary Subunits

This has been a particularly active area of research during the past decade (Coombs and Cull-Candy, 2009; Jackson and Nicoll, 2011; Kato et al., 2010; Straub and Tomita, 2012). The control of neuronal excitability is accomplished by two broad classes of ion channels defined by the way in which they are gated: voltage gated and ligand gated. Molecular cloning of these channels has demonstrated that they are all composed of alpha subunits that form the pore across the membrane. Early studies on the biochemical purification of voltage-gated channels showed that other proteins, which were not a part of the channel pore, copurified with the channel proteins. These smaller auxiliary subunits dictated where, when, and how the channel gets activated. Until recently there was no evidence that ligand-gated channels might also associate with auxiliary subunits. This changed with the discovery of stargazin, the tetraspanning membrane protein mutated in the ataxic mouse stargazer, which is essential for the surface and synaptic expression of AMPARs in cerebellar granule neurons (Chen et al., 2000) (Figure 3). There are at least five other members of this structurally related family of proteins referred to as *t*ransmembrane *A*MPAR *r*egulatory *p*roteins (TARPs). These proteins, which bind to all AMPAR subunits and are differentially expressed throughout the brain, ensure the proper maturation and delivery of AMPARs to the neuron's surface and synapses (Tomita et al., 2003). TARPs contain a PDZ binding ligand and it is proposed that the binding of synaptic MAGUKs to TARPs is responsible for the clustering of AMPARs at the synapse. Furthermore, they alter the gating and pharmacology of AMPARs (Milstein and Nicoll, 2008). Finally, CaMKII and PKC phosphorylate multiple sites on the cytoplasmic C-tails of TARPs, which controls both the constitutive and regulated synaptic trafficking of AMPARs (Sumioka et al., 2010; Tomita et al., 2005). Based on sequence alignment and functional analysis TARPs are further divided into two groups, type I (γ-2, γ-3, γ-4, and γ-8) and type II (γ-5 and γ-7). Type II TARPs are more distantly related to type I and share only some of their functional properties (Kato et al., 2010).

Recent genetic and proteomic screens have identified a number of small proteins that bind to AMPARs and are structurally unrelated to TARPs (Figure 3). These include cornichon-2 and -3 (CNIH-2 and CNIH-3) (Schwenk et al., 2012, 2009), CKAMP44 (von Engelhardt et al., 2010), SynDIG1 (Kalashnikova et al., 2010), GSG1L (Shanks et al., 2012), and in *C. elegans* SOL-1 and SOL-2 (Wang et al., 2012). The most studied of these proteins are CNIH proteins, which profoundly slow the deactivation of AMPARs in heterologous systems (Coombs et al., 2012; Gill et al., 2012; Schwenk et al., 2009; Shi et al., 2010). Genetic deletion of CNIH-2 and -3 together causes a profound and selective loss of synaptic and surface AMPARs in the hippocampus (Herring et al., 2013). This deficit is due to the selective loss of surface GluA1-containing AMPARs (GluA1/A2 heteromers), leaving a small residual pool of synaptic GluA2/A3 heteromers. The kinetics of AMPARs in neurons lacking CNIH-2/-3 are faster than those in WT neurons due to the fast kinetics of GluA2/A3 heteromers. The remarkably selective effect of CNIHs on the GluA1 subunit appears to be mediated by TARP γ-8, which prevents a functional association of CNIHs with non-GluA1 subunits. Surprisingly, although CNIHs strongly slow deactivation in heterologous cells, they do not directly affect the kinetics of surface neuronal AMPARs, indicating either that they dissociate from the AMPARs in the Golgi/ER akin to the chaperoning role of their yeast and *Drosophila* homologs or that their selective binding to surface GluA1 subunits of GluA1/A2 heteromers is functionally silent. These results point to a sophisticated interplay between CNIHs and TARP γ-8 that dictates subunit-specific AMPAR trafficking and the strength and kinetics of synaptic AMPAR-mediated transmission. CKAMP44 is expressed at high levels in dentate granule cells where it enhances AMPAR desensitization and recovery from desensitization, thus impacting short-term plasticity (von Engelhardt et al., 2010).

Neuroligins and Transsynaptic Signaling

Neuroligins (NLs) and leucine-rich repeat transmembrane proteins (LRRTMs) are postsynaptic adhesion molecules that bind to presynaptic neurexins and are involved in excitatory synapses assembly, maturation, and specification (Craig and Kang, 2007; Krueger et al., 2012; Südhof, 2008) (Figure 3). However, recent findings indicate that both NLs and LRRTMs have more specific roles in both AMPAR trafficking and LTP. Knockdown of LRRTM1 and LRRTM2 in CA1 neurons selectively reduces AMPAR-EPSCs in the neonate (Soler-Llavina et al., 2011), although in dentate granule cells the NMDAR-EPSC is also reduced (de Wit et al., 2009). Remarkably, knockin mice constitutively expressing the SS4 splice sequence in presynaptic neurexin-3 have a selective decrease in postsynaptic AMPARs, mostly likely due to its inability to bind to LRRTMs, in contrast to neurexin-3 that lacks the SS4 splice sequence (Aoto et al., 2013). Overexpression of NL3 selectively enhances AMPARs currents, whereas NL1 also enhances NMDAR currents (Shipman et al., 2011). This enhancement is prevented by a single amino acid substitution (E740N) in the proximal cytoplasmic C-tail. Interestingly, another single amino acid substitution in NL3 (R704C) also strongly and selectively impaired AMPAR-EPSCs (Etherton et al., 2011). These findings indicate that specific residues in the proximal C-terminal domain of NL3 are selectively involved in AMPAR trafficking. It will be of interest to determine what intermediate protein(s) link the proximal C terminus of NL3 to the constitutive trafficking of AMPARs. On the other hand, the LRRTMs may interact directly with AMPARs (de Wit et al., 2009; Schwenk et al., 2012).

A recent series of studies have found an unexpected role of NLs and LRRTMs in LTP. The presence of NL1 containing the alternatively spliced B site insertion in the extracellular domain is a requirement for the expression of LTP in young CA1 pyramidal cells (Shipman and Nicoll, 2012). This requirement for NL1 persists into adulthood in the dentate gyrus, where the incorporation of adult born neurons requires ongoing synaptic formation and remodeling. NL3, which lacks the B site insert, is not

required for the support of LTP (Shipman and Nicoll, 2012). In addition to the reduction in the basal trafficking of AMPARs in mice expressing the constitutive SS4 splice sequence in presynaptic neurexin-3, these mice also have a defect in LTP, suggesting that transsynaptic signaling via a neurexin/LRRTM interaction is necessary for LTP (Aoto et al., 2013). In support of this model is the finding that knockdown of LRRTMs block LTP and that the extracellular domain of the LRRTMs is required for LTP (Soler-Llavina et al., 2013). All these findings point to a model in which the presence of NLs and LRRTMs at synapses is required for maintaining synaptic AMPARs and for the expression of LTP. The finding that proteins once thought to be dedicated to a structural and adhesive role in synapse assembly and maturation are also critical for synaptic plasticity raises many exciting questions. We know very little about how these cell adhesion proteins can specifically control AMPAR trafficking and this will be an area of interest going forward.

NMDAR-Dependent LTD

NMDAR-dependent LTD was discovered in 1992 (Dudek and Bear, 1992). For comprehensive reviews on LTD the reader is referred to a number of reviews (Collingridge et al., 2010; Malenka and Bear, 2004; Shepherd and Huganir, 2007). LTD is blocked by the presence of the calcium chelator BAPTA in the postsynaptic cell (Mulkey and Malenka, 1992) and by inhibitors of the phosphatase calcineurin (Mulkey et al., 1994). The difference between LTP and LTD is proposed to be due to the magnitude and duration of the calcium signaling (Lisman, 1989). A most appealing model to account for the ability of a single signal, calcium, to drive bidirectional plasticity is the following (Lisman, 1989; Malenka and Bear, 2004). High levels of calcium activate the low-affinity kinase, CaMKII, to initiate the phosphorylation of PSD proteins, ultimately resulting in enhanced transmission. On the other hand, modest levels of calcium selectively engage the high-affinity phosphatase, calcineurin, resulting in the dephosphorylation of PSD proteins and a reduction in transmission. More specifically, it has been reported that an AKAP150/PSD-95/calcineurin complex is required for LTD (Jurado et al., 2010). In addition, studies have suggested that dephosphorylation of both PKA and PKC substrates, including dephosphorylation of GluA1, are involved in LTD (Lee et al., 1998). Knockin mice containing mutations in the GluA1 CaMKII and PKA phosphorylation sites have significant deficits in LTD, providing compelling evidence that dephosphorylation is important for LTD induction (Lee et al., 2003).

Recent provocative experiments have challenged this well-accepted model of LTD induction. It has been reported that, while competitive antagonists of the NMDARs, such as APV, block LTD, noncompetitive antagonists including the open channel blocker MK-801 and the glycine site antagonist 7-chlorokynurenate (7CK) do not, despite the complete blockade of NMDAR-mediated currents by these antagonists (Nabavi et al., 2013). The authors propose a "metabotropic" action for NMDARs whereby a conformational change in the receptor, independent of ion flux, engages downstream signaling pathways resulting in LTD. How can this model be reconciled with the previous results, i.e., the requirement for postsynaptic calcium and phosphatases? The authors agree that postsynaptic BAPTA blocks LTD. However, when they clamp calcium to basal levels with BAPTA/calcium, LTD is normal, arguing that basal calcium levels are permissive for LTD. They further provide evidence that basal calcium constitutively activates calcineurin and tonically maintains AMPAR transmission at a depressed level. It will be of considerable interest to work out the downstream signaling pathways and how NMDARs engage these pathways.

There is a general consensus that the decrease in synaptic transmission during LTD is due to a loss of synaptic AMPARs. However, although a large number of proteins have been implicated in LTD, no coherent model has emerged. These studies have focused either on modification of the AMPAR C-terminal domains or manipulating signaling molecules. The C-terminal domain of the GluA2 subunit is phosphorylated at S880, which disrupts the interaction of scaffolding proteins with its PDZ ligand and blocks LTD (Kim et al., 2001; Seidenman et al., 2003). However, the fact that LTD is normal in mice lacking both GluA2 and GluA3 indicates that the GluA2 subunit is not essential for LTD (Meng et al., 2003). Interestingly, a knockin mouse in which S845 of the GluA1 subunit is replaced with an alanine is deficient in LTD (Lee et al., 2010). Once again, however, LTD is normal in mice lacking the GluA1 subunit (Selcher et al., 2012). Other signaling molecules have been implicated in LTD including Rap and the p38 MAP kinase (Zhu et al., 2002), the GTPase Arf1 (Rocca et al., 2013), the JAK/STAT signaling pathway (Nicolas et al., 2012), and PI3Kγ (Kim et al., 2011). Unfortunately, despite the large number of manipulations that prevent LTD, it is difficult to link all these findings into a satisfactory model. New approaches are clearly needed to uncover the core molecular underpinnings of LTD.

Cerebellar LTD

Another major model of synaptic plasticity in the brain is LTD at the parallel fiber-Purkinje cell synapse (Hansel and Linden, 2000). Cerebellar LTD, unlike hippocampal LTD, does not require NMDAR activation and is induced by the coincident activation of mGluR1 receptors and voltage-gated calcium channels that in turn activate protein kinase C (De Zeeuw et al., 1998; Linden and Connor, 1991), resulting in synaptic depression. Work in the mid-1990s indicated that the expression of LTD is postsynaptic (Linden, 1994), as it was demonstrated that the sensitivity of Purkinje cells to AMPA was depressed after LTD induction. Inhibitors of endocytosis were found to block LTD (Wang and Linden, 2000), leading to the proposal that PKC increased the endocytosis of AMPARs after LTD induction. With the discovery that AMPARs were phosphorylated by PKC it was proposed that the direct phosphorylation of the GluA2 subunit might be critical for LTD expression (Chung et al., 2000). GluR2 phosphorylation had previously been show to regulate endocytosis and to regulate the interaction of GluA2 with two interacting proteins, GRIP1/2 and PICK1 (Chung et al., 2000; Matsuda et al., 1999). During the past decade the molecular pathways involved in cerebellar LTD were elucidated using a combination of several knockout and knockin mice. First, it was found that cerebellar LTD is subunit dependent and requires the GluA2 subunit and even the GluA3 subunit, which is highly homologous to GluA2, could not support LTD (Chung et al., 2003; Steinberg et al., 2004). Critical regions in the GluA2 subunit involved in cell

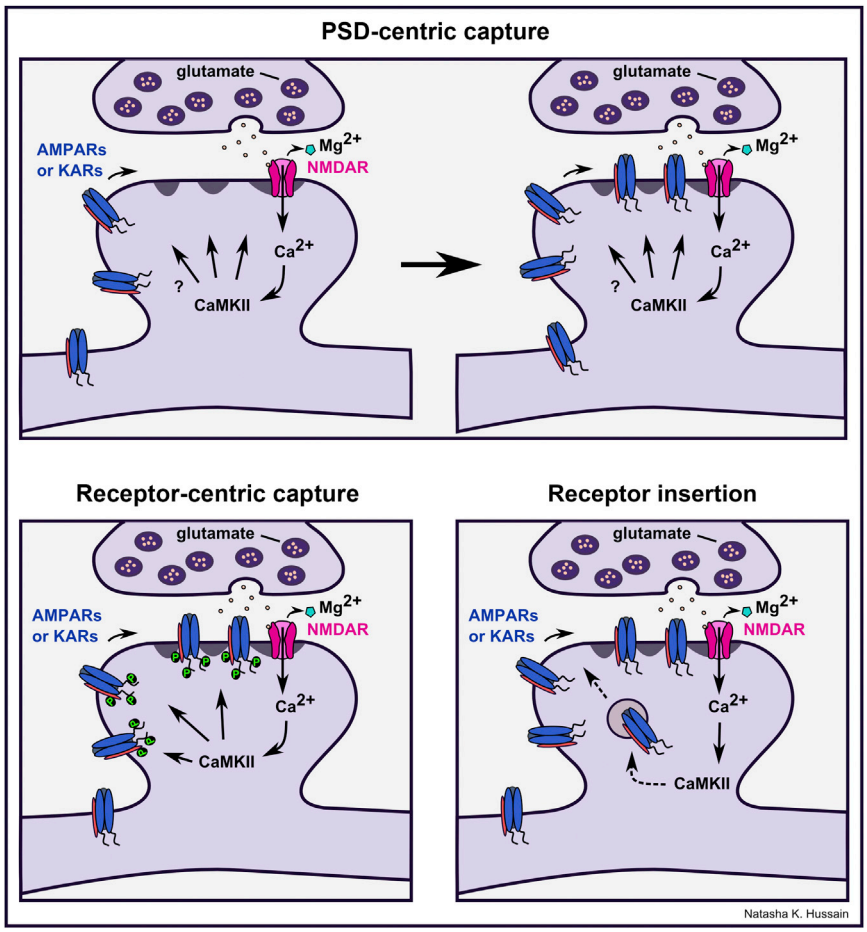

Figure 4. Proposed Working Models for LTP

PSD-centric capture model. In this model CaMKII and downstream signaling cascades act on the PSD to create slots to capture receptors and increase synaptic strength. The identity of these slots is still not known but may involve the MAGUK proteins or other PSD structural proteins. The slots must be rather promiscuous because they are unable to distinguish between AMPARs and kainate receptors.

Receptor-centric capture model. In this model the slots are present at the PSD but are unable to accommodate and trap the receptors. CaMKII and downstream signaling cascades target the receptors and phosphorylates the receptor complex such that the receptors are now captured by the PSD. In this scenario the C-terminal domains would play an important modulatory role but are not essential.

Receptor insertion model. In this model activation of CaMKII acts on membrane trafficking machinery and drives the exocytosis of glutamate receptor-containing vesicles onto the surface, increasing the level of receptors at the synapse and synaptic strength.

membrane trafficking included the C-terminal PKC phosphorylation site as well as a site that interacts with NSF (Steinberg et al., 2004, 2006; Takamiya et al., 2008). In addition, knockout of PICK1 or GRIP1 and 2 eliminated LTD expression (Steinberg et al., 2006; Takamiya et al., 2008). These data led to a model where PKC phosphorylation of GluA2 decreases its interaction with GRIP1/2 and promotes its interaction with PICK1 to help retain intracellular GluA2 (Shepherd and Huganir, 2007).

Interestingly, the orphan AMPAR-like subunit GluD2 (Kashiwabuchi et al., 1995) is also required for LTD even though it does not associate with AMPARs in the cerebellum. The mechanisms underlying the GluD2 requirement are not known but may have to do with its interactions with intracellular trafficking machinery or extracellular transsynaptic proteins, such as clbn1 (Ito-Ishida et al., 2012). Recent studies indicate that GluD2 regulates GluA2 tyrosine 876 and serine 880 phosphorylation (Kohda et al., 2013).

Conclusions and Future Directions

We have made steady progress in our understanding of the molecular mechanisms underlying synaptic plasticity in the last 25 years. However, it is clear that we have a lot more to discover. Major accomplishments have been the general acceptance that hippocampal LTP is expressed as a postsynaptic mechanism triggered by activation of CaMKII and downstream signaling pathways that involve Ras, Rho, and other small G-proteins. Also, it has been recognized that the membrane trafficking of AMPARs is quite dynamic and that increases and decreases in synaptic strength during LTP and LTD, respectively, are mediated by rapid and long-lasting changes in AMPAR number at synaptic spines. The regulation of the membrane trafficking and synaptic retention of AMPARs is quite complex and involves both recruitment of receptors from intracellular pools such as recycling endosomes and also recruitment of receptors from extrasynaptic pools that laterally diffuse into the synapse (Figure 2). These processes are regulated by a large number of proteins that retain and guide the receptors from these nonsynaptic locations and scaffolding proteins that finally retain receptors at the synapse (Figure 3). In addition, extracellular transsynaptic interactions of adhesion-like molecules have recently been implicated in the expression of LTP and add a new layer of complexity (Figure 3). Although there is significant evidence that there are subunit specific rules for AMPAR trafficking during plasticity, recent work has suggested that, although distinct subunits may have a competitive advantage to support LTP, and respond differentially to neuromodulators, they are not absolutely required for LTP. All AMPAR subunits and even kainate receptor subunits can be engaged by LTP signaling pathways and expression mechanisms. This means that, whatever the core mechanism of LTP is, it can act on both AMPARs and kainate receptors. Conceptually, this is hard to explain as these receptors have distinct auxiliary subunits, but they have been reported to have common interacting proteins (Anggono and Huganir, 2012;

Coussen, 2009), suggesting that these shared interactors may be functionally important for LTP.

These new results have challenged the field to come up with new ideas on how these receptors can be recruited and captured at synapses. Future work will need to include the further characterization of the complex receptor recycling pathways and the extrasynaptic pools of receptors. We need to better understand the regulation of these pools during LTP and the molecules involved. In addition, further attention to scaffolding and transsynaptic proteins and their specific role in LTP is required.

Proposed Working Models for LTP

Based on our present knowledge we offer three possible scenarios for how AMPARs might be recruited to the synapse during LTP (Figure 4). These are not mutually exclusive and they assume that CaMKII is both necessary and sufficient. The first model is the capture model (PSD-centric). In this model CaMKII acts on the PSD to create slots. These slots have not been identified and may involve MAGUKs or other structural proteins. These slots must be rather promiscuous because they are unable to distinguish between AMPARs and kainate receptors. AMPARs are known to be highly mobile and can enter and exit the PSD (Opazo and Choquet, 2011). With the addition of new slots, these mobile receptors are captured and held at the synapse. Such an activity-dependent remodeling of the PSD that can capture receptors independent of specific modification of AMPARs is consistent with a mechanism of diffusional trapping of receptors by molecular crowding in the PSD (Renner et al., 2009a, 2009b; Santamaria et al., 2010). This is the most parsimonious of the models but fails to explain some findings that are discussed in the remaining models.

The second model is the capture model (receptor-centric). In this model the slots are present at the PSD but are unable to accommodate and trap the receptors. CaMKII targets the receptors and phosphorylates the receptor complex such that the receptors are now captured by the slots. In this scenario the C-terminal domains would play an important modulatory role but are not essential. Modification of some other domain(s) of the receptor or their auxiliary subunits, either directly or indirectly, would play the essential role. However, this model is not as parsimonious as the first model because it is necessary to propose that CaMKII can also target kainate receptor complexes despite their divergent homology.

The third model is the insertion model. In this model CaMKII drives the exocytosis of glutamate receptor containing vesicles onto the surface. Presumably this would occur perisynaptically, since it is hard to envisage such insertion directly into the PSD. This model is supported by data indicating that blockade of exocytosis by a variety of means blocks LTP (Jurado et al., 2013; Lledo et al., 1998). There are some caveats, which are hard to explain by this model. The first issue is that the AMPAR exocytosis does not require CaMKII (Patterson et al., 2010). Second, it has been reported that from a quantitative standpoint, the receptors recruited to the synapse are largely from the surface pool (Makino and Malinow, 2009; Patterson et al., 2010). Finally, if the exocytotic event is the activity-dependent step, it is unclear how the PSD would distinguish these receptors from the large pool of pre-existing surface receptors. How would these exocytosed receptors be preferentially targeted to the synapse rather than intermingle with the extrasynaptic surface receptor pool?

It is clear from the last 25 years of research that regulation of AMPAR function and membrane trafficking are key to many forms of synaptic plasticity in the brain. This research has identified many molecular and cellular pathways that regulate AMPAR function and are important for not only synaptic plasticity but for learning and memory and behavior. Interestingly, recent genetic studies of schizophrenia, autism, and intellectual disability have implicated many of the same molecules involved in these processes in the etiology of these diseases, indicating that disruption of AMPAR modulation and plasticity is critical for normal cognition in humans.

ACKNOWLEDGMENTS

We would like to thank Natasha Hussain for the design of the figures.

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.

Anggono, V., and Huganir, R.L. (2012). Regulation of AMPA receptor trafficking and synaptic plasticity. Curr. Opin. Neurobiol. *22*, 461–469.

Aoto, J., Martinelli, D.C., Malenka, R.C., Tabuchi, K., and Südhof, T.C. (2013). Presynaptic neurexin-3 alternative splicing trans-synaptically controls postsynaptic AMPA receptor trafficking. Cell *154*, 75–88.

Ascher, P., and Nowak, L. (1988). The role of divalent cations in the N-methyl-D-aspartate responses of mouse central neurones in culture. J. Physiol. *399*, 247–266.

Barria, A., and Malinow, R. (2005). NMDA receptor subunit composition controls synaptic plasticity by regulating binding to CaMKII. Neuron *48*, 289–301.

Barria, A., Muller, D., Derkach, V., Griffith, L.C., and Soderling, T.R. (1997). Regulatory phosphorylation of AMPA-type glutamate receptors by CaM-KII during long-term potentiation. Science *276*, 2042–2045.

Beattie, E.C., Carroll, R.C., Yu, X., Morishita, W., Yasuda, H., von Zastrow, M., and Malenka, R.C. (2000). Regulation of AMPA receptor endocytosis by a signaling mechanism shared with LTD. Nat. Neurosci. *3*, 1291–1300.

Béïque, J.C., and Andrade, R. (2003). PSD-95 regulates synaptic transmission and plasticity in rat cerebral cortex. J. Physiol. *546*, 859–867.

Béïque, J.C., Lin, D.T., Kang, M.G., Aizawa, H., Takamiya, K., and Huganir, R.L. (2006). Synapse-specific regulation of AMPA receptor function by PSD-95. Proc. Natl. Acad. Sci. USA *103*, 19535–19540.

Benke, T.A., Lüthi, A., Isaac, J.T., and Collingridge, G.L. (1998). Modulation of AMPA receptor unitary conductance by synaptic activity. Nature *393*, 793–797.

Blackstone, C.D., Levey, A.I., Martin, L.J., Price, D.L., and Huganir, R.L. (1992). Immunological detection of glutamate receptor subtypes in human central nervous system. Ann. Neurol. *31*, 680–683.

Blackstone, C., Murphy, T.H., Moss, S.J., Baraban, J.M., and Huganir, R.L. (1994). Cyclic AMP and synaptic activity-dependent phosphorylation of AMPA-preferring glutamate receptors. J. Neurosci. *14*, 7585–7593.

Bliss, T.V., and Collingridge, G.L. (2013). Expression of NMDA receptor-dependent LTP in the hippocampus: bridging the divide. Mol. Brain *6*, 5.

Bliss, T.V., and Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J. Physiol. *232*, 331–356.

Boehm, J., Kang, M.G., Johnson, R.C., Esteban, J., Huganir, R.L., and Malinow, R. (2006). Synaptic incorporation of AMPA receptors during LTP is controlled by a PKC phosphorylation site on GluR1. Neuron *51*, 213–225.

Borgdorff, A.J., and Choquet, D. (2002). Regulation of AMPA receptor lateral movements. Nature *417*, 649–653.

Bredt, D.S., and Nicoll, R.A. (2003). AMPA receptor trafficking at excitatory synapses. Neuron *40*, 361–379.

Cai, X., Kallarackal, A.J., Kvarta, M.D., Goluskin, S., Gaylor, K., Bailey, A.M., Lee, H.K., Huganir, R.L., and Thompson, S.M. (2013). Local potentiation of excitatory synapses by serotonin and its alteration in rodent models of depression. Nat. Neurosci. *16*, 464–472.

Carroll, R.C., Lissin, D.V., von Zastrow, M., Nicoll, R.A., and Malenka, R.C. (1999). Rapid redistribution of glutamate receptors contributes to long-term depression in hippocampal cultures. Nat. Neurosci. *2*, 454–460.

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.

Cho, K.O., Hunt, C.A., and Kennedy, M.B. (1992). The rat brain postsynaptic density fraction contains a homolog of the Drosophila discs-large tumor suppressor protein. Neuron *9*, 929–942.

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.

Citri, A., Bhattacharyya, S., Ma, C., Morishita, W., Fang, S., Rizo, J., and Malenka, R.C. (2010). Calcium binding to PICK1 is essential for the intracellular retention of AMPA receptors underlying long-term depression. J. Neurosci. *30*, 16437–16452.

Collingridge, G.L., Kehl, S.J., and McLennan, H. (1983). Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. J. Physiol. *334*, 33–46.

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

Collingridge, G.L., Peineau, S., Howland, J.G., and Wang, Y.T. (2010). Long-term depression in the CNS. Nat. Rev. Neurosci. *11*, 459–473.

Coombs, I.D., and Cull-Candy, S.G. (2009). Transmembrane AMPA receptor regulatory proteins and AMPA receptor function in the cerebellum. Neuroscience *162*, 656–665.

Coombs, I.D., Soto, D., Zonouzi, M., Renzi, M., Shelley, C., Farrant, M., and Cull-Candy, S.G. (2012). Cornichons modify channel properties of recombinant and glial AMPA receptors. J. Neurosci. *32*, 9796–9804.

Coussen, F. (2009). Molecular determinants of kainate receptor trafficking. Neuroscience *158*, 25–35.

Craig, A.M., and Kang, Y. (2007). Neurexin-neuroligin signaling in synapse development. Curr. Opin. Neurobiol. *17*, 43–52.

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.

de Wit, J., Sylwestrak, E., O'Sullivan, M.L., Otto, S., Tiglio, K., Savas, J.N., Yates, J.R., 3rd, Comoletti, D., Taylor, P., and Ghosh, A. (2009). LRRTM2 interacts with Neurexin1 and regulates excitatory synapse formation. Neuron *64*, 799–806.

De Zeeuw, C.I., Hansel, C., Bian, F., Koekkoek, S.K., van Alphen, A.M., Linden, D.J., and Oberdick, J. (1998). Expression of a protein kinase C inhibitor in Purkinje cells blocks cerebellar LTD and adaptation of the vestibulo-ocular reflex. Neuron *20*, 495–508.

Derkach, V., Barria, A., and Soderling, T.R. (1999). Ca2+/calmodulin-kinase II enhances channel conductance of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate type glutamate receptors. Proc. Natl. Acad. Sci. USA *96*, 3269–3274.

Dev, K.K., Nakajima, Y., Kitano, J., Braithwaite, S.P., Henley, J.M., and Nakanishi, S. (2000). PICK1 interacts with and regulates PKC phosphorylation of mGLUR7. J. Neurosci. *20*, 7252–7257.

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.

Dong, H., Zhang, P., Song, I., Petralia, R.S., Liao, D., and Huganir, R.L. (1999). Characterization of the glutamate receptor-interacting proteins GRIP1 and GRIP2. J. Neurosci. *19*, 6930–6941.

Dosemeci, A., and Jaffe, H. (2010). Regulation of phosphorylation at the postsynaptic density during different activity states of Ca2+/calmodulin-dependent protein kinase II. Biochem. Biophys. Res. Commun. *391*, 78–84.

Dudek, S.M., and Bear, M.F. (1992). Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. Proc. Natl. Acad. Sci. USA *89*, 4363–4367.

Ehlers, M.D. (2000). Reinsertion or degradation of AMPA receptors determined by activity-dependent endocytic sorting. Neuron *28*, 511–525.

Ehrlich, I., and Malinow, R. (2004). Postsynaptic density 95 controls AMPA receptor incorporation during long-term potentiation and experience-driven synaptic plasticity. J. Neurosci. *24*, 916–927.

El-Husseini, A.E., Schnell, E., Chetkovich, D.M., Nicoll, R.A., and Bredt, D.S. (2000). PSD-95 involvement in maturation of excitatory synapses. Science *290*, 1364–1368.

Elias, G.M., Funke, L., Stein, V., Grant, S.G., Bredt, D.S., and Nicoll, R.A. (2006). Synapse-specific and developmentally regulated targeting of AMPA receptors by a family of MAGUK scaffolding proteins. Neuron *52*, 307–320.

Etherton, M.R., Tabuchi, K., Sharma, M., Ko, J., and Südhof, T.C. (2011). An autism-associated point mutation in the neuroligin cytoplasmic tail selectively impairs AMPA receptor-mediated synaptic transmission in hippocampus. EMBO J. *30*, 2908–2919.

Gill, M.B., Kato, A.S., Wang, H., and Bredt, D.S. (2012). AMPA receptor modulation by cornichon-2 dictated by transmembrane AMPA receptor regulatory protein isoform. Eur. J. Neurosci. *35*, 182–194.

Gomperts, S.N., Rao, A., Craig, A.M., Malenka, R.C., and Nicoll, R.A. (1998). Postsynaptically silent synapses in single neuron cultures. Neuron *21*, 1443–1451.

Granger, A.J., Shi, Y., Lu, W., Cerpas, M., and Nicoll, R.A. (2013). LTP requires a reserve pool of glutamate receptors independent of subunit type. Nature *493*, 495–500.

Halt, A.R., Dallapiazza, R.F., Zhou, Y., Stein, I.S., Qian, H., Juntti, S., Wojcik, S., Brose, N., Silva, A.J., and Hell, J.W. (2012). CaMKII binding to GluN2B is critical during memory consolidation. EMBO J. *31*, 1203–1216.

Hansel, C., and Linden, D.J. (2000). Long-term depression of the cerebellar climbing fiber—Purkinje neuron synapse. Neuron *26*, 473–482.

Harvey, C.D., and Svoboda, K. (2007). Locally dynamic synaptic learning rules in pyramidal neuron dendrites. Nature *450*, 1195–1200.

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.

Hayashi, T., Thomas, G.M., and Huganir, R.L. (2009). Dual palmitoylation of NR2 subunits regulates NMDA receptor trafficking. Neuron *64*, 213–226.

Herring, B.E., Shi, Y., Suh, Y.H., Zheng, C.Y., Blankenship, S.M., Roche, K.W., and Nicoll, R.A. (2013). Cornichon proteins determine the subunit composition of synaptic AMPA receptors. Neuron *77*, 1083–1096.

Howard, M.A., Elias, G.M., Elias, L.A., Swat, W., and Nicoll, R.A. (2010). The role of SAP97 in synaptic glutamate receptor dynamics. Proc. Natl. Acad. Sci. USA *107*, 3805–3810.

Hu, H., Real, E., Takamiya, K., Kang, M.G., Ledoux, J., Huganir, R.L., and Malinow, R. (2007). Emotion enhances learning via norepinephrine regulation of AMPA-receptor trafficking. Cell *131*, 160–173.

Isaac, J.T., Nicoll, R.A., and Malenka, R.C. (1995). Evidence for silent synapses: implications for the expression of LTP. Neuron *15*, 427–434.

Ito, M., Sakurai, M., and Tongroach, P. (1982). Climbing fibre induced depression of both mossy fibre responsiveness and glutamate sensitivity of cerebellar Purkinje cells. J. Physiol. *324*, 113–134.

Ito-Ishida, A., Miyazaki, T., Miura, E., Matsuda, K., Watanabe, M., Yuzaki, M., and Okabe, S. (2012). Presynaptically released Cbln1 induces dynamic axonal structural changes by interacting with GluD2 during cerebellar synapse formation. Neuron *76*, 549–564.

Jaafari, N., Henley, J.M., and Hanley, J.G. (2012). PICK1 mediates transient synaptic expression of GluA2-lacking AMPA receptors during glycine-induced AMPA receptor trafficking. J. Neurosci. *32*, 11618–11630.

Jackson, A.C., and Nicoll, R.A. (2011). The expanding social network of ionotropic glutamate receptors: TARPs and other transmembrane auxiliary subunits. Neuron *70*, 178–199.

Jahr, C.E., and Stevens, C.F. (1987). Glutamate activates multiple single channel conductances in hippocampal neurons. Nature *325*, 522–525.

Jurado, S., Biou, V., and Malenka, R.C. (2010). A calcineurin/AKAP complex is required for NMDA receptor-dependent long-term depression. Nat. Neurosci. *13*, 1053–1055.

Jurado, S., Goswami, D., Zhang, Y., Molina, A.J., Südhof, T.C., and Malenka, R.C. (2013). LTP requires a unique postsynaptic SNARE fusion machinery. Neuron *77*, 542–558.

Kalashnikova, E., Lorca, R.A., Kaur, I., Barisone, G.A., Li, B., Ishimaru, T., Trimmer, J.S., Mohapatra, D.P., and Díaz, E. (2010). SynDIG1: an activity-regulated, AMPA- receptor-interacting transmembrane protein that regulates excitatory synapse development. Neuron *65*, 80–93.

Kameyama, K., Lee, H.K., Bear, M.F., and Huganir, R.L. (1998). Involvement of a postsynaptic protein kinase A substrate in the expression of homosynaptic long-term depression. Neuron *21*, 1163–1175.

Kashiwabuchi, N., Ikeda, K., Araki, K., Hirano, T., Shibuki, K., Takayama, C., Inoue, Y., Kutsuwada, T., Yagi, T., Kang, Y., et al. (1995). Impairment of motor coordination, Purkinje cell synapse formation, and cerebellar long-term depression in GluR delta 2 mutant mice. Cell *81*, 245–252.

Kato, A.S., Gill, M.B., Yu, H., Nisenbaum, E.S., and Bredt, D.S. (2010). TARPs differentially decorate AMPA receptors to specify neuropharmacology. Trends Neurosci. *33*, 241–248.

Kessels, H.W., and Malinow, R. (2009). Synaptic AMPA receptor plasticity and behavior. Neuron *61*, 340–350.

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.

Kim, J.I., Lee, H.R., Sim, S.E., Baek, J., Yu, N.K., Choi, J.H., Ko, H.G., Lee, Y.S., Park, S.W., Kwak, C., et al. (2011). PI3Kγ is required for NMDA receptor-dependent long-term depression and behavioral flexibility. Nat. Neurosci. *14*, 1447–1454.

Kohda, K., Kakegawa, W., Matsuda, S., Yamamoto, T., Hirano, H., and Yuzaki, M. (2013). The δ2 glutamate receptor gates long-term depression by coordinating interactions between two AMPA receptor phosphorylation sites. Proc. Natl. Acad. Sci. USA *110*, E948–E957.

Kornau, H.C., Schenker, L.T., Kennedy, M.B., and Seeburg, P.H. (1995). Domain interaction between NMDA receptor subunits and the postsynaptic density protein PSD-95. Science *269*, 1737–1740.

Kristensen, A.S., Jenkins, M.A., Banke, T.G., Schousboe, A., Makino, Y., Johnson, R.C., Huganir, R., and Traynelis, S.F. (2011). Mechanism of Ca2+/calmodulin-dependent kinase II regulation of AMPA receptor gating. Nat. Neurosci. *14*, 727–735.

Krueger, D.D., Tuffy, L.P., Papadopoulos, T., and Brose, N. (2012). The role of neurexins and neuroligins in the formation, maturation, and function of vertebrate synapses. Curr. Opin. Neurobiol. *22*, 412–422.

Lee, H.K., Kameyama, K., Huganir, R.L., and Bear, M.F. (1998). NMDA induces long-term synaptic depression and dephosphorylation of the GluR1 subunit of AMPA receptors in hippocampus. Neuron *21*, 1151–1162.

Lee, H.K., Barbarosie, M., Kameyama, K., Bear, M.F., and Huganir, R.L. (2000). Regulation of distinct AMPA receptor phosphorylation sites during bidirectional synaptic plasticity. Nature *405*, 955–959.

Lee, H.K., Takamiya, K., Han, J.S., Man, H., Kim, C.H., Rumbaugh, G., Yu, S., Ding, L., He, C., Petralia, R.S., et al. (2003). Phosphorylation of the AMPA receptor GluR1 subunit is required for synaptic plasticity and retention of spatial memory. Cell *112*, 631–643.

Lee, S.H., Simonetta, A., and Sheng, M. (2004). Subunit rules governing the sorting of internalized AMPA receptors in hippocampal neurons. Neuron *43*, 221–236.

Lee, S.J., Escobedo-Lozoya, Y., Szatmari, E.M., and Yasuda, R. (2009). Activation of CaMKII in single dendritic spines during long-term potentiation. Nature *458*, 299–304.

Lee, H.K., Takamiya, K., He, K., Song, L., and Huganir, R.L. (2010). Specific roles of AMPA receptor subunit GluR1 (GluA1) phosphorylation sites in regulating synaptic plasticity in the CA1 region of hippocampus. J. Neurophysiol. *103*, 479–489.

Leonard, A.S., Davare, M.A., Horne, M.C., Garner, C.C., and Hell, J.W. (1998). SAP97 is associated with the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor GluR1 subunit. J. Biol. Chem. *273*, 19518–19524.

Liao, D., Hessler, N.A., and Malinow, R. (1995). Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. Nature *375*, 400–404.

Liao, D., Zhang, X., O'Brien, R., Ehlers, M.D., and Huganir, R.L. (1999). Regulation of morphological postsynaptic silent synapses in developing hippocampal neurons. Nat. Neurosci. *2*, 37–43.

Liao, D., Scannevin, R.H., and Huganir, R.L. (2001). Activation of silent synapses by rapid activity-dependent synaptic recruitment of AMPA receptors. J. Neurosci. *21*, 6008–6017.

Lin, D.T., Makino, Y., Sharma, K., Hayashi, T., Neve, R., Takamiya, K., and Huganir, R.L. (2009). Regulation of AMPA receptor extrasynaptic insertion by 4.1N, phosphorylation and palmitoylation. Nat. Neurosci. *12*, 879–887.

Linden, D.J. (1994). Input-specific induction of cerebellar long-term depression does not require presynaptic alteration. Learn. Mem. *1*, 121–128.

Linden, D.J., and Connor, J.A. (1991). Participation of postsynaptic PKC in cerebellar long-term depression in culture. Science *254*, 1656–1659.

Lisman, J. (1989). A mechanism for the Hebb and the anti-Hebb processes underlying learning and memory. Proc. Natl. Acad. Sci. USA *86*, 9574–9578.

Lisman, J., Yasuda, R., and Raghavachari, S. (2012). Mechanisms of CaMKII action in long-term potentiation. Nat. Rev. Neurosci. *13*, 169–182.

Lissin, D.V., Gomperts, S.N., Carroll, R.C., Christine, C.W., Kalman, D., Kitamura, M., Hardy, S., Nicoll, R.A., Malenka, R.C., and von Zastrow, M. (1998). Activity differentially regulates the surface expression of synaptic AMPA and NMDA glutamate receptors. Proc. Natl. Acad. Sci. USA *95*, 7097–7102.

Lledo, P.M., Zhang, X., Südhof, T.C., Malenka, R.C., and Nicoll, R.A. (1998). Postsynaptic membrane fusion and long-term potentiation. Science *279*, 399–403.

Lomo, T. (1966). Frequency potentiation of excitatory synaptic activity in the dentate area of the hippocampal formation. Acta Physiol. Scand. *68*, 128.

Lu, W., and Roche, K.W. (2012). Posttranslational regulation of AMPA receptor trafficking and function. Curr. Opin. Neurobiol. *22*, 470–479.

Lu, W., Shi, Y., Jackson, A.C., Bjorgan, K., During, M.J., Sprengel, R., Seeburg, P.H., and Nicoll, R.A. (2009). Subunit composition of synaptic AMPA receptors revealed by a single-cell genetic approach. Neuron *62*, 254–268.

Lüscher, C., and Malenka, R.C. (2012). NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). Cold Spring Harb. Perspect. Biol. *4*, 4.

Lüscher, 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.

Lynch, G., Larson, J., Kelso, S., Barrionuevo, G., and Schottler, F. (1983). Intracellular injections of EGTA block induction of hippocampal long-term potentiation. Nature *305*, 719–721.

Makino, H., and Malinow, R. (2009). AMPA receptor incorporation into synapses during LTP: the role of lateral movement and exocytosis. Neuron *64*, 381–390.

Makino, Y., Johnson, R.C., Yu, Y., Takamiya, K., and Huganir, R.L. (2011). Enhanced synaptic plasticity in mice with phosphomimetic mutation of the GluA1 AMPA receptor. Proc. Natl. Acad. Sci. USA *108*, 8450–8455.

Malenka, R.C., and Bear, M.F. (2004). LTP and LTD: an embarrassment of riches. Neuron *44*, 5–21.

Malenka, R.C., Kauer, J.A., Perkel, D.J., Mauk, M.D., Kelly, P.T., Nicoll, R.A., and Waxham, M.N. (1989). An essential role for postsynaptic calmodulin and protein kinase activity in long-term potentiation. Nature *340*, 554–557.

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

Malinow, R., and Miller, J.P. (1986). Postsynaptic hyperpolarization during conditioning reversibly blocks induction of long-term potentiation. Nature *320*, 529–530.

Malinow, R., Schulman, H., and Tsien, R.W. (1989). Inhibition of postsynaptic PKC or CaMKII blocks induction but not expression of LTP. Science *245*, 862–866.

Mammen, A.L., Kameyama, K., Roche, K.W., and Huganir, R.L. (1997). Phosphorylation of the alpha-amino-3-hydroxy-5-methylisoxazole4-propionic acid receptor GluR1 subunit by calcium/calmodulin-dependent kinase II. J. Biol. Chem. *272*, 32528–32533.

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.

Matsuzaki, M., Honkura, N., Ellis-Davies, G.C., and Kasai, H. (2004). Structural basis of long-term potentiation in single dendritic spines. Nature *429*, 761–766.

Mayer, M.L., Westbrook, G.L., and Guthrie, P.B. (1984). Voltage-dependent block by Mg2+ of NMDA responses in spinal cord neurones. Nature *309*, 261–263.

McGlade-McCulloh, E., Yamamoto, H., Tan, S.-E., Brickey, D.A., and Soderling, T.R. (1993). Phosphorylation and regulation of glutamate receptors by calcium/calmodulin-dependent protein kinase II. Nature *362*, 640–642.

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.

Milstein, A.D., and Nicoll, R.A. (2008). Regulation of AMPA receptor gating and pharmacology by TARP auxiliary subunits. Trends Pharmacol. Sci. *29*, 333–339.

Molnár, E., Baude, A., Richmond, S.A., Patel, P.B., Somogyi, P., and McIlhinney, R.A. (1993). Biochemical and immunocytochemical characterization of antipeptide antibodies to a cloned GluR1 glutamate receptor subunit: cellular and subcellular distribution in the rat forebrain. Neuroscience *53*, 307–326.

Moss, S.J., Blackstone, C.D., and Huganir, R.L. (1993). Phosphorylation of recombinant non-NMDA glutamate receptors on serine and tyrosine residues. Neurochem. Res. *18*, 105–110.

Mulkey, R.M., and Malenka, R.C. (1992). Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. Neuron *9*, 967–975.

Mulkey, R.M., Endo, S., Shenolikar, S., and Malenka, R.C. (1994). Involvement of a calcineurin/inhibitor-1 phosphatase cascade in hippocampal long-term depression. Nature *369*, 486–488.

Murakoshi, H., Wang, H., and Yasuda, R. (2011). Local, persistent activation of Rho GTPases during plasticity of single dendritic spines. Nature *472*, 100–104.

Nabavi, S., Kessels, H.W., Alfonso, S., Aow, J., Fox, R., and Malinow, R. (2013). Metabotropic NMDA receptor function is required for NMDA receptor-dependent long-term depression. Proc. Natl. Acad. Sci. USA *110*, 4027–4032.

Nicolas, C.S., Peineau, S., Amici, M., Csaba, Z., Fafouri, A., Javalet, C., Collett, V.J., Hildebrandt, L., Seaton, G., Choi, S.L., et al. (2012). The Jak/STAT pathway is involved in synaptic plasticity. Neuron *73*, 374–390.

Nicoll, R.A., and Roche, K.W. (2013). Long-term potentiation: Peeling the onion. Neuropharmacology *74*, 18–22.

Nicoll, R.A., Kauer, J.A., and Malenka, R.C. (1988). The current excitement in long-term potentiation. Neuron *1*, 97–103.

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.

Nowak, L., Bregestovski, P., Ascher, P., Herbet, A., and Prochiantz, A. (1984). Magnesium gates glutamate-activated channels in mouse central neurones. Nature *307*, 462–465.

O'Brien, R.J., Kamboj, S., Ehlers, M.D., Rosen, K.R., Fischbach, G.D., and Huganir, R.L. (1998). Activity-dependent modulation of synaptic AMPA receptor accumulation. Neuron *21*, 1067–1078.

Opazo, P., and Choquet, D. (2011). A three-step model for the synaptic recruitment of AMPA receptors. Mol. Cell. Neurosci. *46*, 1–8.

Opazo, P., Sainlos, M., and Choquet, D. (2012). Regulation of AMPA receptor surface diffusion by PSD-95 slots. Curr. Opin. Neurobiol. *22*, 453–460.

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.

Patterson, M.A., Szatmari, E.M., and Yasuda, R. (2010). AMPA receptors are exocytosed in stimulated spines and adjacent dendrites in a Ras-ERK-dependent manner during long-term potentiation. Proc. Natl. Acad. Sci. USA *107*, 15951–15956.

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.

Renner, M., Choquet, D., and Triller, A. (2009a). Control of the postsynaptic membrane viscosity. J. Neurosci. *29*, 2926–2937.

Renner, M.L., Cognet, L., Lounis, B., Triller, A., and Choquet, D. (2009b). The excitatory postsynaptic density is a size exclusion diffusion environment. Neuropharmacology *56*, 30–36.

Rocca, D.L., Amici, M., Antoniou, A., Suarez, E.B., Halemani, N., Murk, K., McGarvey, J., Jaafari, N., Mellor, J.R., Collingridge, G.L., and Hanley, J.G. (2013). The small GTPase Arf1 modulates Arp2/3-mediated actin polymerization via PICK1 to regulate synaptic plasticity. Neuron *79*, 293–307.

Roche, K.W., O'Brien, R.J., Mammen, A.L., Bernhardt, J., and Huganir, R.L. (1996). Characterization of multiple phosphorylation sites on the AMPA receptor GluR1 subunit. Neuron *16*, 1179–1188.

Sanes, J.R., and Lichtman, J.W. (1999). Development of the vertebrate neuromuscular junction. Annu. Rev. Neurosci. *22*, 389–442.

Santamaria, F., Gonzalez, J., Augustine, G.J., and Raghavachari, S. (2010). Quantifying the effects of elastic collisions and non-covalent binding on glutamate receptor trafficking in the post-synaptic density. PLoS Comput. Biol. *6*, e1000780.

Schlüter, O.M., Xu, W., and Malenka, R.C. (2006). Alternative N-terminal domains of PSD-95 and SAP97 govern activity-dependent regulation of synaptic AMPA receptor function. Neuron *51*, 99–111.

Schwenk, J., Harmel, N., Zolles, G., Bildl, W., Kulik, A., Heimrich, B., Chisaka, O., Jonas, P., Schulte, U., Fakler, B., and Klöcker, N. (2009). Functional

proteomics identify cornichon proteins as auxiliary subunits of AMPA receptors. Science *323*, 1313–1319.

Schwenk, J., Harmel, N., Brechet, A., Zolles, G., Berkefeld, H., Müller, C.S., Bildl, W., Baehrens, D., Hüber, B., Kulik, A., et al. (2012). High-resolution proteomics unravel architecture and molecular diversity of native AMPA receptor complexes. Neuron *74*, 621–633.

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.

Selcher, J.C., Xu, W., Hanson, J.E., Malenka, R.C., and Madison, D.V. (2012). Glutamate receptor subunit GluA1 is necessary for long-term potentiation and synapse unsilencing, but not long-term depression in mouse hippocampus. Brain Res. *1435*, 8–14.

Seol, G.H., Ziburkus, J., Huang, S., Song, L., Kim, I.T., Takamiya, K., Huganir, R.L., Lee, H.K., and Kirkwood, A. (2007). Neuromodulators control the polarity of spike-timing-dependent synaptic plasticity. Neuron *55*, 919–929.

Shanks, N.F., Savas, J.N., Maruo, T., Cais, O., Hirao, A., Oe, S., Ghosh, A., Noda, Y., Greger, I.H., Yates, J.R., 3rd, and Nakagawa, T. (2012). Differences in AMPA and kainate receptor interactomes facilitate identification of AMPA receptor auxiliary subunit GSG1L. Cell Rep. *1*, 590–598.

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

Shepherd, J.D., and Huganir, R.L. (2007). The cell biology of synaptic plasticity: AMPA receptor trafficking. Annu. Rev. Cell Dev. Biol. *23*, 613–643.

Shi, S.H., Hayashi, Y., Petralia, R.S., Zaman, S.H., Wenthold, R.J., Svoboda, K., and Malinow, R. (1999). Rapid spine delivery and redistribution of AMPA receptors after synaptic NMDA receptor activation. Science *284*, 1811–1816.

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.

Shi, Y., Suh, Y.H., Milstein, A.D., Isozaki, K., Schmid, S.M., Roche, K.W., and Nicoll, R.A. (2010). Functional comparison of the effects of TARPs and cornichons on AMPA receptor trafficking and gating. Proc. Natl. Acad. Sci. USA *107*, 16315–16319.

Shipman, S.L., and Nicoll, R.A. (2012). A subtype-specific function for the extracellular domain of neuroligin 1 in hippocampal LTP. Neuron *76*, 309–316.

Shipman, S.L., Schnell, E., Hirai, T., Chen, B.S., Roche, K.W., and Nicoll, R.A. (2011). Functional dependence of neuroligin on a new non-PDZ intracellular domain. Nat. Neurosci. *14*, 718–726.

Soderling, T.R. (1993). Calcium/calmodulin-dependent protein kinase II: role in learning and memory. Mol. Cell. Biochem. *127-128*, 93–101.

Soler-Llavina, G.J., Fuccillo, M.V., Ko, J., Südhof, T.C., and Malenka, R.C. (2011). The neurexin ligands, neuroligins and leucine-rich repeat transmembrane proteins, perform convergent and divergent synaptic functions in vivo. Proc. Natl. Acad. Sci. USA *108*, 16502–16509.

Soler-Llavina, G.J., Arstikaitis, P., Morishita, W., Ahmad, M., Südhof, T.C., and Malenka, R.C. (2013). Leucine-rich repeat transmembrane proteins are essential for maintenance of long-term potentiation. Neuron *79*, 439–446.

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.

Srivastava, S., and Ziff, E.B. (1999). ABP: a novel AMPA receptor binding protein. Ann. N Y Acad. Sci. *868*, 561–564.

Steinberg, J.P., Huganir, R.L., and Linden, D.J. (2004). N-ethylmaleimide-sensitive factor is required for the synaptic incorporation and removal of AMPA receptors during cerebellar long-term depression. Proc. Natl. Acad. Sci. USA *101*, 18212–18216.

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.

Straub, C., and Tomita, S. (2012). The regulation of glutamate receptor trafficking and function by TARPs and other transmembrane auxiliary subunits. Curr. Opin. Neurobiol. *22*, 488–495.

Südhof, T.C. (2008). Neuroligins and neurexins link synaptic function to cognitive disease. Nature *455*, 903–911.

Sumioka, A., Yan, D., and Tomita, S. (2010). TARP phosphorylation regulates synaptic AMPA receptors through lipid bilayers. Neuron *66*, 755–767.

Swope, S.L., Moss, S.J., Blackstone, C.D., and Huganir, R.L. (1992). Phosphorylation of ligand-gated ion channels: a possible mode of synaptic plasticity. FASEB J. *6*, 2514–2523.

Takamiya, K., Mao, L., Huganir, R.L., and Linden, D.J. (2008). The glutamate receptor-interacting protein family of GluR2-binding proteins is required for long-term synaptic depression expression in cerebellar Purkinje cells. J. Neurosci. *28*, 5752–5755.

Takumi, Y., Ramírez-León, V., Laake, P., Rinvik, E., and Ottersen, O.P. (1999). Different modes of expression of AMPA and NMDA receptors in hippocampal synapses. Nat. Neurosci. *2*, 618–624.

Tan, S.-E., Wenthold, R.J., and Soderling, T.R. (1994). Phosphorylation of AMPA-type glutamate receptors by calcium/calmodulin-dependent protein kinase II and protein kinase C in cultured hippocampal neurons. J. Neurosci. *14*, 1123–1129.

Terashima, A., Pelkey, K.A., Rah, J.C., Suh, Y.H., Roche, K.W., Collingridge, G.L., McBain, C.J., and Isaac, J.T. (2008). An essential role for PICK1 in NMDA receptor-dependent bidirectional synaptic plasticity. Neuron *57*, 872–882.

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., Stein, V., Stocker, T.J., Nicoll, R.A., and Bredt, D.S. (2005). Bidirectional synaptic plasticity regulated by phosphorylation of stargazin-like TARPs. Neuron *45*, 269–277.

Traynelis, S.F., Wollmuth, L.P., McBain, C.J., Menniti, F.S., Vance, K.M., Ogden, K.K., Hansen, K.B., Yuan, H., Myers, S.J., and Dingledine, R. (2010). Glutamate receptor ion channels: structure, regulation, and function. Pharmacol. Rev. *62*, 405–496.

Turrigiano, G.G. (2008). The self-tuning neuron: synaptic scaling of excitatory synapses. Cell *135*, 422–435.

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.

Volk, L., Kim, C.H., Takamiya, K., Yu, Y., and Huganir, R.L. (2010). Developmental regulation of protein interacting with C kinase 1 (PICK1) function in hippocampal synaptic plasticity and learning. Proc. Natl. Acad. Sci. USA *107*, 21784–21789.

von Engelhardt, J., Mack, V., Sprengel, R., Kavenstock, N., Li, K.W., Stern-Bach, Y., Smit, A.B., Seeburg, P.H., and Monyer, H. (2010). CKAMP44: a brain-specific protein attenuating short-term synaptic plasticity in the dentate gyrus. Science *327*, 1518–1522.

Wang, Y.T., and Linden, D.J. (2000). Expression of cerebellar long-term depression requires postsynaptic clathrin-mediated endocytosis. Neuron *25*, 635–647.

Wang, R., Mellem, J.E., Jensen, M., Brockie, P.J., Walker, C.S., Hoerndli, F.J., Hauth, L., Madsen, D.M., and Maricq, A.V. (2012). The SOL-2/Neto auxiliary protein modulates the function of AMPA-subtype ionotropic glutamate receptors. Neuron *75*, 838–850.

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

Wigström, H., Gustafsson, B., Huang, Y.Y., and Abraham, W.C. (1986). Hippocampal long-term potentiation is induced by pairing single afferent volleys with intracellularly injected depolarizing current pulses. Acta Physiol. Scand. *126*, 317–319.

Wyllie, D.J., and Nicoll, R.A. (1994). A role for protein kinases and phosphatases in the Ca(2+)-induced enhancement of hippocampal AMPA receptor-mediated synaptic responses. Neuron *13*, 635–643.

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.

Xu, W. (2011). PSD-95-like membrane associated guanylate kinases (PSD-MAGUKs) and synaptic plasticity. Curr. Opin. Neurobiol. *21*, 306–312.

Xu, W., Schlüter, O.M., Steiner, P., Czervionke, B.L., Sabatini, B., and Malenka, R.C. (2008). Molecular dissociation of the role of PSD-95 in regulating synaptic strength and LTD. Neuron *57*, 248–262.

Yoshimura, Y., Aoi, C., and Yamauchi, T. (2000). Investigation of protein substrates of Ca(2+)/calmodulin-dependent protein kinase II translocated to the postsynaptic density. Brain Res. Mol. Brain Res. *81*, 118–128.

Yoshimura, Y., Shinkawa, T., Taoka, M., Kobayashi, K., Isobe, T., and Yamauchi, T. (2002). Identification of protein substrates of Ca(2+)/calmodulin-dependent protein kinase II in the postsynaptic density by protein sequencing and mass spectrometry. Biochem. Biophys. Res. Commun. *290*, 948–954.

Zheng, C.Y., Seabold, G.K., Horak, M., and Petralia, R.S. (2011). MAGUKs, synaptic development, and synaptic plasticity. Neuroscientist *17*, 493–512.

Zhou, Y., Takahashi, E., Li, W., Halt, A., Wiltgen, B., Ehninger, D., Li, G.D., Hell, J.W., Kennedy, M.B., and Silva, A.J. (2007). Interactions between the NR2B receptor and CaMKII modulate synaptic plasticity and spatial learning. J. Neurosci. *27*, 13843–13853.

Zhu, J.J., Qin, Y., Zhao, M., Van Aelst, L., and Malinow, R. (2002). Ras and Rap control AMPA receptor trafficking during synaptic plasticity. Cell *110*, 443–455.