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Synaptic plasticity and phosphorylation

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Abstract

A number of neuronal functions, including synaptic plasticity, depend on proper regulation of synaptic proteins, many of which can be rapidly regulated by phosphorylation. Neuronal activity controls the function of these synaptic proteins by exquisitely regulating the balance of various protein kinase and protein phosphatase activity. Recent understanding of synaptic plasticity mechanisms underscores important roles that these synaptic phosphoproteins play in regulating both pre- and post-synaptic functions. This review will focus on key postsynaptic phosphoproteins that have been implicated to play a role in synaptic plasticity.

Keywords

Phosphoproteins; Postsynaptic; Long-term potentiation; Long-term depression; Homeostatic plasticity

1. Introduction

Activity-dependent changes in synaptic connections are considered critical in many of the brain functions, ranging from developmental plasticity, memory formation, recovery of function after injury, drug addiction, to neurodegeneration. Synaptic plasticity can result from both external (i.e. experience) and internal (i.e. developmental) factors, however this review will focus on synapse changes induced by experience, in the form of neural activity. Bidirectional modifications of synaptic strength can be elicited experimentally using electrical stimulation paradigms in diverse set of synapses in various brain regions (Malenka & Bear, 2004), and also has been observed in vivo following learning (Rogan et al., 1997; Rioult-Pedotti et al., 2000) or sensory experience (Sawtell et al., 2003; Clem & Barth, 2006; Goel et al., 2006). It is now recognized that there are largely 2 classes of synaptic plasticity mechanisms that are required for proper neural function. One form of synaptic plasticity operates on specific sets of synapses (i.e. synapse-specific plasticity), while another set is loosely bound together under the terminology “homeostatic plasticity”, which acts on global variables to affect the function of all synapses on a given neuron. Therefore, investigations of the molecular mechanisms of synaptic plasticity require an understanding of the type of plasticity that is being studied.

Alterations in synaptic strength, either by synapse-specific plasticity or homeostatic plasticity, can be mediated by multiple mechanisms. First, changes can be at synaptic loci, both pre- and postsynaptic compartments. Second, it can be mediated by changes in dendritic or axonal excitability. Third, synaptic plasticity can result from alterations in gene expression, again in either pre- or postsynaptic neurons. Lastly, non-neuronal changes can also contribute, for example changes in glial–neuronal interactions or vascular–neuronal interactions. However,

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discussion of all these topics would be beyond the scope of this review, and thus the following discussion will be limited to how regulation of key postsynaptic proteins contributes to changes in synaptic strength. There are now vast amounts of data, which implicate reversible phosphorylation of synaptic proteins as a potential mechanism for mediating various forms of synaptic plasticity. Most of the results come from studies of synapse-specific plasticity mechanisms, such as long-term potentiation (LTP) and long-term depression (LTD). However, increasing number of recent studies is focusing on understanding the molecular mechanisms of homeostatic plasticity.

2. A brief introduction to synaptic plasticity

It was recognized early on that activity-dependent changes in the efficacy of synapses could be a mechanism for information storage, particularly in learning and memory formation. Donald O. Hebb is credited with the first formulation of a learning rule based on correlated neural activity. He proposed that synaptic connections become stronger when the presynaptic activity triggers action potentials in the postsynaptic neuron (Hebb, 1949). The Hebbian rule was first confirmed 2 decades later by the discovery that brief and intense synaptic activation results in a LTP of synaptic strength in the hippocampus (Bliss & Lomo, 1973). Subsequently, the necessity for an anti-Hebbian rule in which synaptic strength decreases when the activity of the 2 neurons are not correlated was also recognized (Stent, 1973). This was confirmed nearly 2 decades later when several investigators demonstrated that delivering prolonged but weak subthreshold stimulation results in a LTD of synaptic strength in the hippocampus (Fujii et al., 1991; Dudek & Bear, 1992; Mulkey & Malenka, 1992). More recently, premises of both Hebbian and anti-Hebbian mode of synaptic plasticity have been tested by demonstration of spike-timing dependent plasticity (STDP) where the timing between pre- and post-synaptic activity determines the sign of synaptic change (for a review on STDP, see Dan & Poo, 2004). For a more comprehensive historic overview on the 30 years of research on LTP and LTD, readers are referred to volume 358, issue 1432 of the *Philosophical Transactions of the Royal Society of London Series B Biological Sciences* (*Philos Trans R Soc Lond B Biol Sci*).

The discovery of LTP and LTD opened the possibility of understanding the basic cellular and molecular mechanisms of synaptic plasticity. It is now clear that several forms of LTP and LTD can be induced in almost all areas of the central nervous system. However, most of our understanding on the molecular mechanisms of synaptic plasticity derives from studies on a specific form of LTP and LTD, which is dependent on *N*-methyl-$_{D}$-aspartate (NMDA) receptor activation. Due to the intense research efforts of the last few decades, the basic properties and induction mechanisms of LTP and LTD have been worked out to considerable biophysical and molecular detail. Currently, rapid progress is being made in elucidating the cellular changes that express synaptic plasticity, and how these changes are maintained for a prolonged duration. There is accumulating evidence that changes in protein phosphorylation by various protein kinases and protein phosphatases are involved in either mediating or regulating LTP and LTD expression. This will be elaborated upon in the following section.

It has been appreciated for some time that rapid bidirectional synaptic plasticity mechanisms, such as LTP and LTD, are not sufficient to mediate proper brain function (Bienenstock et al., 1982a; Bear et al., 1987; Abraham & Bear, 1996; Miller, 1996; Turrigiano & Nelson, 2000, 2004). This is due to the fact that LTP and LTD have a built-in positive-feedback mechanism that causes instability in a neural network (for recent reviews on this topic, see Turrigiano & Nelson, 2000, 2004). There are several mechanisms proposed that can provide negative feedback to stabilize synapse-specific synaptic plasticity. One is the “sliding threshold” model, which proposed that the threshold for inducing LTP and LTD “slides” as a function of average postsynaptic activity (Bienenstock et al., 1982b; Bear, 1995). An overall increase in output activity will “slide” the “threshold” to favor LTD induction, while a decrease in average output

activity will “slide” the “threshold” to favor LTP induction. A mechanism termed “priming”, where prior history of synaptic activity alters subsequent synaptic plasticity, is also considered to result from “sliding threshold”. Often, the “sliding threshold” model is referred to as “metaplasticity” to emphasize that it is a plasticity mechanism for regulating synaptic plasticity (Abraham & Bear, 1996). A second mechanism of homeostatic plasticity is termed “synaptic scaling”, where chronic increase in input activity “scales down” the strength of all synapses impinging on a neuron, while a persistent decrease in input activity “scales up” all the synapses (Turrigiano et al., 1998; Turrigiano & Nelson, 2004).

“Sliding threshold” or “metaplasticity” is thought to involve changes in the molecular events that regulate LTP and LTD induction mechanisms. For example, changes in NMDA receptor function has been suggested as 1 mechanism for “metaplasticity” at synapses that undergo NMDA receptor-dependent LTP and LTD (Quinlan, Olstein et al., 1999; Quinlan, Philpot et al., 1999; Philpot et al., 2001; Philpot et al., 2003). On the other hand, “synaptic scaling” has been linked to regulation of both α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors (Lissin et al., 1998; O'Brien et al., 1998; Turrigiano et al., 1998; Ju et al., 2004; Thiagarajan et al., 2005) and NMDA receptors (Watt et al., 2000), as well as changes in postsynaptic excitability (Maffei et al., 2004), inhibition (Rutherford et al., 1998), and presynaptic function (Burrone et al., 2002; Thiagarajan et al., 2002, 2005). Regardless of the terminologies and the underlying mechanisms, net effect of homeostatic plasticity is to provide stability to neural networks that constantly undergo synapse-specific modifications.

3. Protein kinases and protein phosphatases involved in synaptic plasticity: a short introduction

Despite divergence in details, there is a general consensus that NMDA receptor-dependent LTP and LTD are triggered by postsynaptic mechanisms. The magnitude and temporal pattern of increase in postsynaptic calcium through NMDA receptors seems to be the key in determining whether LTP or LTD is induced (Cummings et al., 1996; Yang et al., 1999). This is thought to be due to the differential sensitivity of protein kinases and protein phosphatases to calcium increase (Lisman, 1985). Various protein kinases and protein phosphatases have been implicated in synaptic plasticity, and many are in close proximity to NMDA receptors (Husi et al., 2000), ideally suited to mediate the downstream signaling by the activation of this receptor.

The identity of the exact protein kinases and phosphatases required for LTP and LTD is still under debate. For LTP, there is evidence for the involvement of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), protein kinase C (PKC), cAMP-dependent protein kinase (PKA), cGMP-dependent protein kinase (PKG), casein kinase II (CKII), mitogen-activated protein kinase (MAPK), various tyrosine kinases, and regulation of various protein phosphatases (see Table 1). As for LTD, activity of various protein phosphatases (protein phosphatase 1 [PP1], protein phosphatase 2A [PP2A], protein phosphatase 2B [PP2B, calcineurin]; see Table 1) and regulation of PKA (Brandon et al., 1995;Kameyama et al., 1998) and PKC (Thiels et al., 2000) are implicated.

It seems unlikely, however, that all these molecules are essential for LTP and LTD expression. More likely many of them may play a modulatory or permissive role in the induction or may control the duration of long-term synaptic plasticity (for a more detailed discussion, refer to Sanes & Lichtman, 1999). Indeed in many cases, the involvement of a given protein kinase and protein phosphatase in LTP and LTD appears to depend on the stimulation protocols employed in each study or on the history of prior synaptic activation. Detailed discussions on the many proposed roles of each protein kinases and protein phosphatases in synaptic plasticity are beyond the scope of this review. Readers interested in this topic are referred to some review

papers that are focused on this topic (Roberson et al., 1996; Brandon et al., 1997; Ramakers et al., 1997; Blanquet, 2000; Soderling, 2000; Sweatt, 2001; Winder & Sweatt, 2001; Lisman et al., 2002; Nguyen & Woo, 2003; Colbran & Brown, 2004; Kalia et al., 2004; Thomas & Huganir, 2004; Feil et al., 2005). Here I will only provide a brief synopsis on generally agreed functions of some of the protein kinases implicated in synaptic plasticity (see Table 1 for more details).

One particularly fruitful hypothesis on the mechanism of LTP and LTD was proposed by Lisman in 1987. This hypothesis rests on the critical properties of 2 enzymes, CaMKII and PP2B, both of which are activated by Ca^{2+}. CaMKII can phosphorylate itself upon activation and become independent of Ca^{2+}. PP2B can eventually dephosphorylate CaMKII through a protein phosphatase cascade. Importantly, PP2B has a higher affinity for Ca^{2+}/calmodulin than CaMKII. Thus, moderate increases in Ca^{2+} will preferentially activate PP2B, and eventually dephosphorylate and inactivate CaMKII. Larger increases in Ca^{2+}, on the other hand, will promote CaMKII autophosphorylation. If the proportion of autophosphorylated CaMKII somehow codes for synaptic strength, it follows that moderate increases in Ca^{2+} will result in LTD, while a large increase in Ca^{2+} will produce LTP. This hypothesis, coined as the "CaMKII hypothesis" (Lisman, 1994), has since received much attention, and has been vigorously tested by many laboratories as will be discussed later (see Section 6). The "CaMKII hypothesis" has since been updated to include more recent findings on the functional regulation of synaptic AMPA receptors by this protein kinase (Lisman & Zhabotinsky, 2001; Lisman et al., 2002; also see Sections 8 and 9.1 for discussions on the role of CaMKII in regulating synaptic AMPA receptor trafficking during LTP).

Another protein kinase that is thought to be important for LTP is PKA. Initially PKA was proposed as being important for the maintenance of late-phase LTP (L-LTP) (Matthies & Reymann, 1993; Huang & Kandel, 1994; Qi et al., 1996) or "gating" LTP induction by regulating PP1 activity (Blitzer et al., 1995, 1998; Brown et al., 2000). In lieu of recent data on direct phosphorylation and regulation of AMPA receptor subunits (Roche et al., 1996; Benke et al., 1998; Lee et al., 2000; Zhu et al., 2000; Esteban et al., 2003; Lee et al., 2003; Oh et al., 2006; see Section 8 for more details), it seems PKA may also be more directly involved in the expression of LTP. In addition, PKA can regulate NMDA receptor function (Raman et al., 1996; Krupp et al., 2002; Skeberdis et al., 2006; see Section 5.2 for more details), which can also affect the induction of LTP and/or LTD.

As for other protein kinases, their involvement in the early expression phase of LTP is not clear. Consensus for the functional role of PKC, which has been highly discussed as being critical for LTP, is likely for maintaining stable LTP expression (see Table 1). However, in light of its role in regulating NMDA receptors and neurogranin/RC3, PKC could also participate in setting the induction threshold for LTP and/or LTD (see Section 5.2.1 for a more detailed discussion on NMDA receptor regulation and Section 7 for discussions on neurogranin/RC3).

MAPK signaling cascade has also surfaced to participate in LTP, however, its involvement seems to depend partly on the stimulation paradigm used for LTP induction (Table 1). There is a large body of data suggesting that activation of MAPK pathway leads to transcriptional regulation, which may be required for the late-phase LTP (reviewed in Sweatt, 2001;Thomas & Huganir, 2004). More recent findings suggest that MAPK signaling cascade may also operate more locally at synapses (for a detailed discussion on this topic refer to Thomas & Huganir, 2004).

As for tyrosine kinases, Src and Fyn in particular, their major role seems to be on regulation of NMDA receptors as will be discussed later (see Section 5.1 and Table 1). Therefore, they are likely to participate in modulating the threshold for inducing LTP and/or LTD.

4. Phosphoproteins at synapses

Recently, the first large scale mapping of synaptic phosphoproteins was performed by Collins et al. (2005), which employed a combination of mass spectrometry and other high throughput protein analysis methods to generate a list of phosphoproteins present at synapses. This study identified 79 synaptic phosphoproteins, which collectively have 331 phosphorylation sites in total (Collins et al., 2005). However, whether all these phosphoproteins play a role in synaptic plasticity has yet to be confirmed. In addition, the screen may not identify phosphoproteins that are not phosphorylated under basal conditions and only become phosphorylated by synaptic activity or proteins that traffic in and out of synapses dependent on their phosphorylation state. This review will focus on some of the postsynaptic phosphoproteins that have been implicated in synaptic plasticity (Table 1 lists some of the presynaptic phosphoproteins implicated in synaptic plasticity as well).

5. NMDA receptors

Activation of NMDA receptors is critical for the induction of LTP and LTD at diverse sets of synapses (Malenka & Bear, 2004) and is involved in some forms of homeostatic plasticity (Perez-Otano & Ehlers, 2005). Functional importance of NMDA receptors in mediating synaptic plasticity is that they can act as a coincidence detector and allows influx of calcium, which can be used to activate a variety of signaling cascades. The ability of NMDA receptors to act as coincidence detectors of pre- and post-synaptic activity is due to a voltage-dependent relieve of a Mg^{2+} block of the ion channel (Mayer et al., 1984; Nowak et al., 1984), which allows NMDA receptors to be activated only when presynaptic glutamate release coincides with sufficient postsynaptic depolarization. NMDA receptor channels are formed by tetrameric assembly of 2 obligatory NR1 subunits and 2 NR2 subunits (Cull-Candy et al., 2001). Although majority of the receptors seem to contain a single type of NR2 subunit, it has recently been discussed that NMDA receptors can form triheteromeric receptors with NR1/NR2A/NR2B composition in certain brain areas (Neyton & Paoletti, 2006). There are currently 4 different types of NR2 subunits (i.e. NR2A, NR2B, NR2C, and NR2D) that confer distinct property to the NMDA receptor channel (Cull-Candy et al., 2001). Signaling through NMDA receptors is likely mediated by tightly interacting proteins that comprise a large complex signaling network, often referred to as the “NMDA receptor multiprotein (or macromolecular) complex (NRC)” (Husi et al., 2000) or as the “Hebbosome” (Husi & Grant, 2001). One mode of regulating NMDA receptor function is by phosphorylation of its subunits. Many phosphorylation sites have been identified on the intracellular carboxy-tail of NMDA receptor subunits (Table 2). However, as will be discussed further, some regulation of NMDA receptor function is probably not due to direct phosphorylation of the receptor subunits, but by indirect regulation via other phosphoproteins present in the NMDA receptor macromolecular complex.

NMDA receptor regulation has been suggested to be important for metaplasticity (Abraham & Bear, 1996), because this receptor is critical for the induction of LTP and LTD. The degree of NMDA receptor activation and a subsequent increase in postsynaptic Ca^{2+} concentration usually determines the sign of synaptic plasticity. Therefore, subtle alterations in NMDA receptor function can result in modifying the threshold level of activity required for the induction of LTP or LTD. In accordance with this idea, partial blockade of NMDA receptor or modifying the postsynaptic voltage to allow differential NMDA receptor activation results in sliding the threshold for synaptic plasticity (Cummings et al., 1996; Froemke et al., 2005). This means that partial inhibition of NMDA receptor function can change LTP inducing stimuli

to produce LTD, and enhancement of NMDA receptor function can result in LTP with LTD induction protocols. In extreme cases, down-regulation of NMDA receptor function would completely block the induction of LTP and LTD, making synapses resistant to modification by activity. In addition, regulation of NMDA receptor subunit composition may also selectively inhibit LTP or LTD. A couple of studies demonstrated that induction of LTP is prevented by selective inhibition of NR2A containing receptors, while LTD is abolished by blocking NR2B containing receptors (Liu et al., 2004; Massey et al., 2004). However, these findings have recently been contested by several researchers (Hendricson et al., 2002; Barria & Malinow, 2005; Berberich et al., 2005; Weitlauf et al., 2005; Neyton & Paoletti, 2006). Despite the debates on the exact role of each NR2 subunits in synaptic plasticity, NR2A and NR2B display preferential affinity to different postsynaptic density (PSD) proteins (Sans et al., 2000), which may allow for distinct signaling. Therefore, mechanisms that selectively reduce the function of NR2A- or NR2B-containing NMDA receptors have a potential to specifically alter the recruitment of specific signaling pathways during LTP or LTD.

It is important to note that regulation of NMDA receptor by phosphorylation is dependent on the developmental stage of the neurons and the brain region. In addition, there is evidence that prior history of activity may change the subunit composition, adding another level of complexity in terms of understanding the regulation of NMDA receptors. NR1 splice variants, which can be differentially regulated by phosphorylation, show distinct expression pattern in the nervous system (reviewed in Zukin & Bennett, 1995). In addition, a recent study suggests that synaptic activity may regulate the alternative splicing event (Mu et al., 2003). Different NR2 subunits also show distinct temporal and spatial expression pattern (Williams et al., 1993; Monyer et al., 1994). Among the NR2 subunits, NR2A and NR2B are most highly expressed in the forebrain structures, including hippocampus and cortex (Monyer et al., 1994). It is has been demonstrated that synaptic activity can differentially up- or down-regulate these 2 subunits leading to a change in NR2A to NR2B ratio (Quinlan, Olstein et al., 1999; Quinlan, Philpot et al., 1999; Philpot et al., 2001; Barria & Malinow, 2002; Quinlan et al., 2004; Barria & Malinow, 2005). Since NR2A has a shorter duration current compared to NR2B (Monyer et al., 1994), changes in NR2A/NR2B ratio affects the summation of NMDA receptor-mediated synaptic current during repetitive stimulation (Philpot et al., 2001).

5.1. Regulation of NMDA receptor function by tyrosine phosphorylation

It has been appreciated for some time that an ongoing balance between protein tyrosine kinase (PTK) and protein tyrosine phosphatase (PTP) activity seems necessary for maintaining NMDA receptor function. Application of PTK inhibitors (Wang & Salter, 1994; Wang et al., 1996) or introducing exogenous PTP (Wang et al., 1996) depresses NMDA receptor current. In addition, postsynaptic application of exogenous PTK, especially the Src family of PTK (i.e. Src and Fyn), potentiates NMDA receptor current (Wang & Salter, 1994). Most of the Src family of PTK (i.e. Src, Fyn, Yes, and Lyn) are found in the PSD associated with the NMDA receptor (Salter & Kalia, 2004). Among the PTK, Src has surfaced as the major PTK regulating basal NMDA receptor function, and its activity is thought to be counteracted by an ongoing activity of a PTP called striatal enriched tyrosine phosphatase (STEP) (reviewed in Salter & Kalia, 2004). Both Src and STEP are components of the NMDA receptor macromolecular complex (Yu et al., 1997; Pelkey et al., 2002), ideally suited to regulate the channel activity and, ultimately, synaptic plasticity.

5.1.1. Potential mechanisms of Src family of protein tyrosine kinases in mediating enhancement of NMDA receptor function—

Evidence supporting a role for Src in regulating NMDA receptor function and synaptic plasticity is abundant. Intracellular application of Src potentiates NMDA receptor current (Wang & Salter, 1994), while a Src-specific inhibitory peptide decreases NMDA receptor function (Yu et al., 1997). Src is activated

by LTP-inducing stimulation, and inhibiting Src prevents LTP induction (Lu et al., 1998). Moreover, post-synaptic application of exogenous Src induces synaptic potentiation, that is dependent on NMDA receptor activation, and occludes further LTP (Lu et al., 1998).

Src-mediated potentiation of NMDA receptor function may be due to direct phosphorylation of NMDA receptor subunits. Although the obligatory subunit NR1 does not show detectable tyrosine phosphorylation (Lau & Huganir, 1995), both NR2A and NR2B subunits contain several tyrosine residues on their carboxyl-termini that can be phosphorylated by the Src family of PTK (see Table 2). Src-mediated potentiation of NMDA receptor function is likely mediated by tyrosine phosphorylation of NR2A (Zheng et al., 1998), since Src only potentiates current through NR1/NR2A, but not NR1/NR2B, NR1/NR2C, or NR1/NR2D, expressed in heterologous cells (Kohr & Seeburg, 1996). Several tyrosine phosphorylation sites that are targeted by Src have been identified to potentiate NMDA receptor current by reducing tonic Zn^{2+} inhibition (Zheng et al., 1998). However, whether this mechanism operates in vivo has been challenged (Xiong et al., 1999). Interestingly, Src-mediated potentiation of NMDA receptor seems to depend on the presence of PSD95 (Liao et al., 2000; Iwamoto et al., 2004), suggesting that other PSD proteins may play a role in mediating this effect.

Surface trafficking of NMDA receptors is also regulated by tyrosine phosphorylation. Surface trafficking of NMDA receptors is regulated by tyrosine-based internalization signal motifs (YXXϕ:ϕ corresponding to a bulky hydrophobic residue) that are present on both NR2A and NR2B (Roche et al., 2001; Vissel et al., 2001; Prybylowski et al., 2005). Tyrosine-based internalization motifs bind to a subunit of adaptor protein AP-2, which recruits them to clathrin coats involved in endocytic vesicle formation (Bonifacino & Traub, 2003). The critical internalization motif for NR2A and NR2B appears to be on different locations of the intracellular C-tail, and the regulation of these 2 subunits occurs via slightly different mechanisms.

In the case of NR2B, YEKL sequence that is located on the distal C-terminal, only a few amino acids upstream of the PSD95 discs-large ZO-1 domain (PDZ) ligand ($ESDV_{COOH}$), is critical for internalization (Roche et al., 2001; Prybylowski et al., 2005). The YEKL sequence on NR2B is sufficient to constitutively internalize receptors unless the Y1472 on YEKL sequence is phosphorylated by Fyn or if NR2B is bound to PSD95 via its PDZ ligand (Roche et al., 2001; Prybylowski et al., 2005). It is hypothesized that NR2B binding to PSD95 brings Fyn close to the NR2B YEKL sequence to phosphorylate Y1472 (Prybylowski et al., 2005). This phosphorylation in turn prevents AP-2 adaptors from binding to the YEKL sequence, hence blocking internalization. Increase in tyrosine phosphorylation of NR2B subunits has been observed following LTP induction (Rosenblum et al., 1996; Rostas et al., 1996), which could be the basis for the increased surface NMDA receptor following LTP (Grosshans et al., 2002). However, whether the LTP-induced increase in NR2B tyrosine phosphorylation occurs on Y1472 is unknown. Moreover, the function of the LTP-induced increase in NR2B tyrosine phosphorylation is unclear, since maintenance of LTP is not affected by blocking NMDA receptors (Herron et al., 1986). Also, whether or when NMDA receptor function is potentiated following LTP is debated (Kauer et al., 1988; Clark & Collingridge, 1995; Watt et al., 2004). In any case, synaptic NR2B subunits bound to PSD95 will have an increase in Y1472 phosphorylation, which stabilizes them on the surface. On the other hand, extrasynaptic NMDA receptors are not likely associated with PSD95, which predicts that this population of NMDA receptors may undergo rapid internalization. Consistent with this idea, Roche et al. (2001) observed a developmental decline in constitutive NMDA receptor endocytosis that correlated with developmental increase in PSD95 (Sans et al., 2000).

Unlike the NR2B subunit, endocytosis of NR2A does not depend on the distal YXXϕ motif (Y_{1454}KKM) located on an equivalent position to that of YEKL on NR2B (Lavezzari et al.,

2004; Prybylowski et al., 2005). A more proximal sequence on NR2A carboxy-tail (Y_{842}WKL), closer to the last transmembrane domain, has been implicated as an internalization motif (Vissel et al., 2001). Despite the difference in location, internalization of NR2A is also regulated by phosphorylation of the key tyrosine residue (Y842) on the internalization motif, which prevents AP-2 interaction (Vissel et al., 2001). NR2A-Y842 residue is phosphorylated by Src (Vissel et al., 2001). Phosphorylation of Y842 then allows Src to bind, and this competitive binding seems to block AP-2 interaction (Vissel et al., 2001). Interestingly, tyrosine dephosphorylation-induced internalization of NR1/NR2A complex was independent of channel activation, and only required agonist binding (Vissel et al., 2001). This suggests that down-regulation of NMDA receptors can happen in the absence of its channel activity. However, internalization of NR2A may be a bit more complicated, since a more recent study suggests a dileucine motif ($L_{1319}L_{1320}$) on NR2A may serve as an internalization motif (Lavezzari et al., 2004). How the 2 motifs (Y_{842}WKL and dileucine motifs) interact to regulate NR2A surface expression is currently unknown.

5.1.2. Role of striatal enriched tyrosine phosphatase tyrosine phosphatase in regulating NMDA receptor function—STEP family of non-receptor PTP are highly expressed in the basal ganglia, but also show lower levels of expression in other brain regions, including the hippocampus (Boulanger et al., 1995). Inhibiting STEP enhances basal NMDA receptor current, while postsynaptic injection of exogenous STEP depresses it (Pelkey et al., 2002). In line with its role in counteracting Src activity, blocking Src abolishes the enhancement of NMDA receptor function by STEP inhibition (Pelkey et al., 2002). In accordance with its role in regulating NMDA receptor activity, exogenous STEP application into CA1 neurons prevents LTP induction, while inhibiting STEP produces Src-dependent synaptic potentiation that further occludes LTP (Pelkey et al., 2002). STEP-induced potentiation was blocked by NMDA receptor antagonist, MK801, further suggesting that potentiation of AMPA receptor-mediated synaptic transmission by this enzyme involves the regulation of NMDA receptor activity.

5.2. Regulation of NMDA receptor function by serine phosphorylation

In addition to phosphorylation on tyrosine residues, NMDA receptor subunits can be regulated by phosphorylation on serine residues. PKA and PKC can directly phosphorylate serine residues on NR1, NR2A, and NR2B subunits (Leonard & Hell, 1997; Tingley et al., 1997; Table 2).

5.2.1. Regulation of serine phosphorylation on NR1 subunit—The phosphorylation sites on NR1 have been mapped to serine-890 and serine-896, which are phosphorylated by PKC, and serine-897, which is phosphorylated by PKA (Tingley et al., 1997; Table 2). Phosphorylation of serine-890 by PKC causes dispersion of surface NR1 in heterologous cells (Tingley et al., 1997), which could be a basis for PKC-induced dispersal of synaptic NMDA receptor to extrasynaptic sites (Fong et al., 2002). This contradicts with the more widespread observation that PKC up-regulates NMDA receptor function (reviewed in Ben-Ari et al., 1992). However, it is unlikely that phosphorylation of PKC sites on NR1 subunits plays a role in PKC-mediated potentiation of NMDA receptor currents, because PKC-induced potentiation was still present in mutant receptors either lacking NR1 phosphorylation region (Sigel et al., 1994) or lacking intracellular domains of both NR1 and NR2A (Zheng et al., 1999). PKC-mediated NMDA receptor potentiation may be due to PKC regulation of Src (reviewed in Salter & Kalia, 2004), phosphorylation of NR2B subunit (Liao et al., 2001), or phosphorylation of other regulatory proteins (Lan et al., 2001). Direct phosphorylation of PKC sites on NR1 may have a distinct role in regulating NMDA receptor function.

Different PKC phosphorylation sites on NR1 have been shown to be substrates for specific PKC isoforms (Table 2). For instance, phosphorylation of NR1 serine-896 is preferentially lowered by specific inhibitors for PKC-alpha, while NR1 serine-890 was decreased by a specific peptide inhibitor of PKC-gamma (Sanchez-Perez & Felipo, 2005). PKC-gamma is associated with NR1 (Suen et al., 1998), placing it at an ideal location for regulating NMDA receptors. Application of an mGluR5 (a member of the Group 1 metabotropic glutamate receptor [mGluR]) agonist DHPG (3,5-dihydroxy-phenylglycine) predominantly activates PKC-gamma, but not PKC-alpha or PKC-beta, and increases NR1 serine-890 phosphorylation (Sanchez-Perez & Felipo, 2005). This is interesting in light of the observations that prior mGluR activation prevents subsequent LTP induction (Gisabella et al., 2003;Naie & Manahan-Vaughan, 2004). It is tantalizing to speculate that this effect might be due to PKC-gamma phosphorylation of NR1 serine-890, which would disperse synaptic NMDA receptors to prevent subsequent LTP induction. However, it is important to point out that the effect of Group 1 mGluR activation is quite complex in that activation of this receptor can also enhance LTP induction by a phenomenon called “priming” (Cohen & Abraham, 1996). The seemingly opposite effects of Group 1 mGluR activation on LTP may have to do with the downstream signaling pathway it recruits. The “priming” effect of mGluR activation seems to be linked to phospholipase C (PLC) activation (Cohen et al., 1998) rather than PKC (but see Miura et al., 2002), and depends on up-regulation of translation (Raymond et al., 2000). Moreover, “priming” may not be mediated by direct regulation of NMDA receptor function, since it occurs without changes in basal NMDA receptor synaptic responses (Cohen & Abraham, 1996). As will be discussed later, another PKC substrate, neurogranin/RC3, may be involved in “priming” of LTP (see Section 7).

Recent studies found that NMDA receptor trafficking from endoplasmic reticulum (ER) is dependent on PKC and PKA phosphorylation around the ER retention motif, RXR, present on certain isoforms of NR1 that contain the C1 splicing cassette (Scott et al., 2001, 2003). Serine residues 896 and 897 present on the C1 cassette of NR1 are highly phosphorylated in the microsome fraction that contains ER and Golgi (Scott et al., 2003). The phosphorylation on the serine-897 by PKA is necessary to trigger release from the ER, but the ER exit also depends on the PKC-mediated phosphorylation of other sites (either serine-890 or serine-897) (Scott et al., 2001, 2003). This suggests that a coordinated signaling between PKA and PKC pathways is needed for proper trafficking of NMDA receptors to the plasma membrane. This mechanism may be used to regulate the number of NMDA receptors exiting the ER, which will determine the surface NMDA receptor population. ER exit of NMDA receptors is promoted by alternative splicing of C2′ and C2 splice cassettes present on the NR1 carboxy-terminal (Mu et al., 2003). Interestingly, this splicing event is regulated by synaptic activity (Mu et al., 2003), providing another level of control for this ER exit check point event.

5.2.2. Regulation of serine phosphorylation on NR2 subunits—CaMKII is one of the key NMDA receptor interacting signaling molecules involved in synaptic plasticity. The interaction between active CaMKII and NR2 subunits is thought to be critical for NMDA receptor-dependent LTP expression (Lisman & Zhabotinsky, 2001; Lisman et al., 2002; Barria & Malinow, 2005). This interaction can be modulated by phosphorylation of NR2A and NR2B subunits (Table 2). CaMKII phosphorylation of NR2B-S1303 (Omkumar et al., 1996) promotes dissociation of CaMKII-alpha from NR2B (Strack et al., 2000). This may act as a negative feedback where further recruitment of active CaMKII to synapses causes dissociation of NR2B–CaMKII complexes already present. The interaction between NR2A and CaMKII, which is a weaker interaction than NR2B and CaMKII (Barria & Malinow, 2005), may also be regulated by phosphorylation. Stimulation of slices with a Group 1 mGluR agonist decreases CaMKII-alpha interaction with the NMDA receptor (Gardoni et al., 2001), which may be mediated by PKC phosphorylation of NR2A at S1416 (Gardoni et al., 2001). This result also highlights a potential mechanism for crosstalk between PKC and CaMKII signaling.

NR2 subunits also interact with PSD proteins that contain PDZ domain structures. This interaction occurs by binding of the PDZ proteins to the extreme C-terminus that conforms to a type I PDZ ligand. In the NR2B subunit, serine-1480 present in the PDZ ligand ($ESDV_{COOH}$) has been shown to be a phosphorylation site that can regulate binding of PDZ proteins, and endocytosis of NMDA receptors (Chung et al., 2004). NR2B-S1480 is directly phosphorylated by CKII, but requires activation of NMDA receptor and CaMKII upstream (Chung et al., 2004). The consequence of NR2B-S1480 phosphorylation is a reduced interaction with PSD95 and synapse associated protein 102 (SAP102) (Chung et al., 2004). This provides an attractive mechanism for down-regulating synaptic NMDA receptors by activity. It is known that LTP increases CKII activity (Charriaut-Marlangue et al., 1991). This suggests that LTP induction may increase NR2B-S1480 phosphorylation and allow endocytosis of synaptic NMDA receptors. This in turn will prevent further LTP induction, which may be a homeostatic mechanism to prevent run-away potentiation. It is known LTP saturates upon multiple bouts of high frequency stimulation. Whether phosphorylation of NR2B-S1480 is involved in this process will be of interest. Alternatively, or possibly in conjunction with this, NR2B-S1480 phosphorylation may be involved in LTD. It is known that LTD-inducing stimulation not only depresses AMPA receptor-mediated synaptic transmission, but also NMDA receptor-mediated synaptic transmission (termed "LTD_{NMDAR}") (Xiao et al., 1995; Morishita et al., 2005). Whether the removal of synaptic NMDA receptors via NR2B-S1480 phosphorylation contributes to the LTD_{NMDAR} also awaits confirmation.

6. Ca^{2+}/calmodulin-dependent protein kinase II

CaMKII is a major constituent of the PSD (Kennedy et al., 1983; Walikonis et al., 2000; Peng et al., 2004). CaMKII has received much attention as one of the major protein kinases involved in various forms of synaptic plasticity. CaMKII-alpha and CaMKII-beta are the 2 major isoforms expressed in the brain, which assemble together to make a dodecameric holoenzyme (Kolodziej et al., 2000; Lisman et al., 2002; Colbran & Brown, 2004). CaMKII holoenzyme in vivo exists as either homomeric CaMKII-alpha or heteromeric complexes of CaMKII-alpha and CaMKII-beta (Brocke et al., 1999). Although CaMKII-alpha and CaMKII-beta associate to form a holoenzyme complex, they are expressed differently during development and display slightly different properties and function. For instance, CaMKII-beta is expressed early in development while CaMKII-alpha expression increases dramatically during postnatal development (Bayer et al., 1999). CaMKII-beta, but not the alpha isoform, can regulate neurite extension and synapse formation (Fink et al., 2003). In addition, the ratio of CaMKII-alpha to CaMKII-beta is regulated by activity, such that chronic increase in activity increases CaMKII-alpha/CaMKII-beta ratio, while a persistent decrease activity decreases this ratio (Thiagarajan et al., 2002). Since CaMKII-beta is responsible for attaching CaMKII holoenzyme to the actin cytoskeleton under resting conditions (Shen et al., 1998), changes in CaMKII-alpha/CaMKII-beta ratio will affect subcellular localization of the holoenzyme.

In addition to being a protein kinase, CaMKII is a phosphoprotein and its activity is regulated by autophosphorylation on distinct sites. Autophosphorylation at Threonine-286 (Threonine-287 in CaMKIIbeta), which lies on the autoinhibitory domain of the enzyme, allows constitutive activation of the enzyme (Lai et al., 1986; Miller & Kennedy, 1986; Schworer et al., 1986; Schworer et al., 1988; Thiel et al., 1988). There are also 2 inhibitory phosphorylation sites, Theronine-305 and Threonine-306, which are present on the calmodulin binding region. As will be discussed in more detail, phosphorylation of all these sites has been implicated to play a role in synaptic plasticity.

Vast array of data suggest that CaMKII activity is critical for the induction of NMDA receptor-dependent LTP. Blocking CaMKII activity pharmacologically or via genetic knockout of the CaMKII gene prevents or greatly inhibits LTP (Malenka et al., 1989; Malinow et al., 1989;

Silva et al., 1992; Otmakhov et al., 1997; Hinds et al., 1998; Frankland et al., 2001; Elgersma et al., 2002), and CaMKII is activated by LTP inducing stimuli (Fukunaga et al., 1993, 1995; Barria, Muller et al., 1997; Ouyang et al., 1997; De Koninck & Schulman, 1998; Ouyang et al., 1999). Moreover, postsynaptic injection of constitutively active CaMKII can mimic and occlude LTP (Pettit et al., 1994; Lledo et al., 1995).

6.1. Activation and synaptic targeting of CaMKII by autophosphorylation

In the late 1980's, Lisman proposed a model, which later became known as the "CaMKII hypothesis" of synaptic memory storage (Lisman, 1994). The original idea dwells on the observation that CaMKII can be activated by Ca^{2+} influx through NMDA receptors, which leads to autophosphorylation at Threonine-286 making the enzyme constitutively active (Miller & Kennedy, 1986). This Ca^{2+}-independent CaMKII activity was thought to leave a long-lasting trace or "memory" of the transient increase in intracellular Ca^{2+} (Lisman, 1989, 1994). Interestingly, CaMKII is preferentially activated by high frequency oscillations of intracellular Ca^{2+} (De Koninck & Schulman, 1998), making this molecule an ideal candidate that can be activated by high frequency repetitive stimulation often used for inducing LTP. The autophosphorylation of CaMKII at T286 converts the enzyme to become constitutively active by preventing the autoinhibitory domain from blocking the substrate binding site (discussed in Lisman et al., 2002). A persistent increase in T286 autophosphorylation has been observed following LTP inducing protocols by various laboratories (Barria, Muller et al., 1997; Ouyang et al., 1997; Blitzer et al., 1998; Ouyang et al., 1999; Ahmed & Frey, 2005). This autophosphorylation is critical for the induction of NMDA receptor-dependent LTP, since mutating the T286 site completely blocks this form of LTP (Giese et al., 1998; Hardingham et al., 2003). On the other hand, mimicking this autophosphorylation by mutating Threonine-286 to aspartate (CaMKII-T286D) facilitates LTP induction (Bejar et al., 2002). However, this effect is dependent on the expression level of the transgene, where higher expression levels of the CaMKII-T286D actually prevent LTP and shifts the threshold of synaptic plasticity to favor LTD (Mayford et al., 1995; Bejar et al., 2002). This may suggest that CaMKII activation plays a dual role, one for LTP induction and another for regulating the synaptic plasticity threshold. The proportion of CaMKII phosphorylated on T286 may regulate the latter, likely by affecting the inhibitory autophosphorylation as will be discuss in the next section.

Autophosphorylation at T286 not only produces a constitutively active CaMKII, it also allows the holoenzyme to become tightly associated to the PSD on dendritic spines (reviewed by Fink and Meyer, 2002). Attachment of activated CaMKII molecules to the PSD is achieved by its interaction with NMDA receptors at the PSD (Strack & Colbran, 1998; Gardoni et al., 1999; Leonard et al., 1999; Strack et al., 2000; Bayer et al., 2006). Translocation of CaMKII to dendritic spines by NMDA receptor activation has been visualized in neurons by expressing green fluorescence protein (GFP)-CaMKII fusion proteins (Shen & Meyer, 1999; Shen et al., 2000; Otmakhov et al., 2004; Bayer et al., 2006). T286 autophosphorylation is not necessary for translocation of CaMKII to synapses, but it greatly prolongs the PSD localization of the translocated CaMKII (Shen et al., 2000; Bayer et al., 2006). This phenomenon is often described as CaMKII synaptic "trapping" (Shen et al., 2000; Fink & Meyer, 2002). It has been proposed that the recruitment of activated CaMKII (i.e. CaMKII "trapping") to the PSD provides sites for anchoring AMPA receptors to synapses following LTP induction (Lisman & Zhabotinsky, 2001; Lisman et al., 2002). This hypothesis is supported by the observation that active CaMKII allows for synaptic insertion of AMPA receptors (Hayashi et al., 2000), which will be discussed more in detail in a later section (Section 8).

Autophosphorylation also occurs on the CaMKII-beta subunit at T287(Schworer et al., 1988), which causes dissociation of CaMKII-beta and the CaMKII-beta containing holoenzyme complex from the actin cytoskeleton (Shen & Meyer, 1999). Autophosphorylation

of isolated CaMKII-beta is activated by a lower Ca^{2+}/CaM concentration compared to CaMKII-alpha (Brocke et al., 1999). However, autophosphorylation of CaMKII-beta isolated from rat forebrain requires similar Ca^{2+}/CaM concentration to CaMKII-alpha, suggesting that T287 in the beta subunit is probably phosphorylated by alpha subunits present in the same holoenzyme complex (Brocke et al., 1999).

6.2. Inhibitory autophosphorylation of CaMKII

In addition to T286 autophosphorylation, CaMKII is regulated by 2 inhibitory autophosphorylation sites (Threonine-305 and Threonine-306) present in the Ca^{2+}/calmodulin binding site of the enzyme (Hashimoto et al., 1987; Patton et al., 1990). These 2 inhibitory autophosphorylation sites are only exposed after Ca^{2+}/calmodulin complex dissociates following autophosphorylation at T286 (Hashimoto et al., 1987; Patton et al., 1990). The inhibitory autophosphorylation decreases the CaMKII affinity towards Ca^{2+}/calmodulin (Lickteig et al., 1988; Lou & Schulman, 1989; Colbran, 1993), hence prevents further activation of the enzyme by a subsequent increase in intracellular Ca^{2+}. In addition, phosphorylation of the inhibitory sites reduces the CaMKII affinity to the PSD (Strack, Choi et al., 1997; Shen et al., 2000; Elgersma et al., 2002). These inhibitory autophosphorylation sites seem to regulated the threshold for inducing synaptic plasticity rather than being directly involved in the expression mechanisms of LTP or LTD (Elgersma et al., 2002; Zhang et al., 2005).

Interestingly, association of CaMKII to NMDA receptors hinders inhibitory autophosphorylation (Elgersma et al., 2002), and hence can lock the enzyme in an active state (Bayer et al., 2001). This suggests a plausible mechanism to explain how CaMKII may participate in both LTP and metaplasticity. For instance, initial increase in Ca^{2+} by LTP-inducing stimuli will increase autophosphorylation on T286 and allow CaMKII to bind NMDA receptors, most likely the NR2B subunit (Barria & Malinow, 2005). This interaction between CaMKII and NR2B is critical for LTP expression (Barria & Malinow, 2005). However, if more CaMKII is activated, some will not be able to bind NMDA receptors. And further, these active CaMKII may phosphorylate NR2B subunits (Omkumar et al., 1996) to release pre-bound CaMKII molecules (Strack et al., 2000). All of these changes will promote inhibitory autophosphorylation, hence reducing the pool size of CaMKII that can be activated by subsequent synaptic activity. This in essence will “slide” the threshold for future plasticity.

7. Neurogranin/RC3

Neurogranin is a calmodulin (CaM) binding postsynaptic protein that is also known as RC3, P17 or BICKS (B-50 immunoreactive C-kinase substrate). Neurogranin was identified as a substrate of PKC in the brain (Baudier et al., 1989), and is expressed in postsynaptic compartments of various forebrain structures (Represa et al., 1990; Watson et al., 1992). Subcellular fractionation showed that neurogranin is a soluble protein loosely associated with the PSD (Watson et al., 1994). Interestingly, phosphorylation of neurogranin is regulated by LTP- and LTD-inducing stimuli (Chen et al., 1997; van Dam et al., 2002), and neurogranin knockouts display abnormal synaptic plasticity (Pak et al., 2000; Krucker et al., 2002; Huang et al., 2004).

An interesting key feature of neurogranin is that it binds free calmodulin (Deloulme et al., 1991), and many of its functions can be explained by its ability to regulate the availability of calmodulin in the postsynaptic compartment. Binding of Ca^{2+}-free calmodulin molecules to neurogranin will act to lower the concentration of available calmodulin. Since neurogranins can release calmodulin when intracellular Ca^{2+} increases, it in essence acts as a calmodulin reservoir that only releases calmodulin when the Ca^{2+} concentration crosses a certain threshold (discussed in Chakravarthy et al., 1999). Therefore, neurogranin is able to regulate the activity of postsynaptic Ca^{2+}/CaM-dependent enzymes, one of which is CaMKII. In support of this,

neurogranin knockouts have less autophosphorylated CaMKII than wildtype mice (Pak et al., 2000; Krucker et al., 2002). The interaction between neurogranin and calmodulin is disrupted by phosphorylation of the calmodulin binding domain on neurogranin by PKC (Gerendasy et al., 1995; Prichard et al., 1999), which provides a link between PKC and CaMKII signaling. Among the various PKC isoforms present at synapses, PKC-gamma is likely crucial for neurogranin phosphorylation in vivo, because depolarization and glutamate-induced neurogranin phosphorylation was absent in PKC-gamma knockout mice (Ramakers et al., 1999).

A current understanding of the role of neurogranin in regulating synaptic plasticity is that it regulates the availability of calmodulin for various Ca^{2+}/CaM-dependent signaling molecules. The release of calmodulin by Ca^{2+} influx is enhanced when PKC is concurrently activated, providing a synergistic regulation of Ca^{2+}/CaM-dependent signaling. This would suggest that neurogranin will affect the induction processes of synaptic plasticity, which agrees with the observation that neurogranin knockouts display altered threshold for inducing LTP and LTD (Pak et al., 2000; Krucker et al., 2002; Huang et al., 2004). However, it is puzzling that 2 different lines of neurogranin knockouts display an opposite phenotype in regards to sliding the synaptic plasticity threshold. One group reported that neurogranin knockouts display larger LTP and no LTD, consistent with an interpretation that the modification threshold is slid to the left favoring LTP induction (Krucker et al., 2002). Another group demonstrated using an independent line of neurogranin knockouts that LTP is less, while LTD is larger, suggesting a slide in modification threshold to the right (Huang et al., 2004). This difference was speculated to be due to the presence or absence of the N-terminal fragment of neurogranin in the knockouts (Huang et al., 2004). However, it is equally likely that knockout of neurogranin would affect the activity of a network of signaling pathways (Wu et al., 2003); hence a quite different outcome could result from slight biases in each signaling pathways in the background strain.

8. AMPA receptors

AMPA receptors are ionotropic glutamate receptors comprised of 4 different subunits GluR1–4 (or GluR-A through D) that assemble in a combinatorial fashion to form a functional receptor channel (Nakanishi et al., 1990; Wenthold et al., 1992, 1996). These receptors are the major mediator of fast glutamatergic excitatory synaptic transmission in the central nervous system. Structural studies suggest that tetrameric assembly of AMPA receptors are achieved in a dimer-of-dimers fashion (reviewed in Madden, 2002). Different subunits of AMPA receptors display distinct spatial and temporal pattern of expression, and endow specific properties to AMPA receptor complexes. For example, the GluR2 subunit undergoes RNA editing (reviewed in Seeburg & Hartner, 2003), which prevents Ca^{2+} permeability, contributes to a linear I–V relationship of current flux, and confers insensitivity to intracellular spermine (Boulter et al., 1990; Hollmann et al., 1991; Verdoorn et al., 1991; Keller et al., 1992; Bowie & Mayer, 1995; Donevan & Rogawski, 1995; Washburn et al., 1997). All 4 subunits of AMPA receptors have several identified phosphorylation sites on their intracellular carboxy termini that regulate their function (reviewed in Song & Huganir, 2002), and many more are currently being characterized (Lee et al., 2002; Boehm et al., 2006; Table 3). Due to the essential role of AMPA receptors in mediating synaptic transmission, many of its phosphorylation sites seem to play a role in mediating various forms of synaptic plasticity.

8.1. Phosphorylation of GluR1 subunit

GluR1 is one of the more abundantly expressed subunit of AMPA receptors in hippocampal and neocortical neurons (Martin et al., 1993; Wenthold et al., 1996). Most of the phosphorylation on GluR1 occurs on serine and threonine residues (Blackstone et al., 1994; Roche et al., 1996; Mammen et al., 1997), but tyrosine phosphorylation has also been observed under certain circumstances (Moss et al., 1993; Wu et al., 2004; Table 3). There are several

characterized phosphorylation sites on the intracellular carboxy-terminal of GluR1 (Roche et al., 1996; Barria, Derkach et al., 1997; Mammen et al., 1997; Lee et al., 2002; Boehm et al., 2006). Among these, serine-831 and serine-845 have been implicated to mediate the expression of LTP and LTD (Barria, Muller et al., 1997; Kameyama et al., 1998; Lee et al., 1998, 2000, 2003). Phosphorylation on GluR1-S831 is mediated by PKC and CaMKII (Roche et al., 1996; Barria, Derkach et al., 1997; Mammen et al., 1997), while GluR1-S845 is phosphorylated by PKA (Roche et al., 1996). Phosphorylation on both of these residues can enhance current through AMPA receptor channels, albeit via distinct mechanisms (Derkach et al., 1999; Banke et al., 2000).

Phosphorylation of both GluR1-S831 (Barria, Muller et al., 1997; Lee et al., 2000, 2003) and GluR1-S845 (Lee et al., 2000, 2003; Esteban et al., 2003) has been suggested to mediate LTP expression. Interestingly, the specific phosphorylation site involved seems to depend on the prior history of synaptic activity (Lee et al., 2000). Consistent with these observations, LTP was significantly reduced in adult mice lacking the 2 phosphorylation sites (Lee et al., 2003). However, that some LTP is still present in mice lacking both S831 and S845 phosphorylation sites indicate that phosphorylation events are perhaps not critical for LTP, but may be required for stabilizing LTP (Lee et al., 2003; for more discussion, see Lee, 2006). Taken together with the results demonstrating that adult GluR1 knockout mice do not display LTP (Zamanillo et al., 1999; Mack et al., 2001), this suggests that there are at least 2 components to LTP in adults: one that depends on the presence of GluR1, and another that is dependent on the phosphorylation of the subunit. More recently, mice lacking only S831 or S845 phosphorylation sites were characterized, and preliminary results showed quite normal LTP in both lines (Lee et al., 2004). This suggests that while phosphorylation of S831 and S845 on GluR1 are critical to maintain stable LTP, one or the other is probably sufficient to mediate this function.

The exact role of GluR1-S831 phosphorylation in LTP is unclear at this point. Phosphorylation of GluR1-S831 by CaMKII increases single channel conductance (Derkach et al., 1999), hence it was initially thought to mediate the observed increase in AMPA receptor conductance following LTP induction (Benke et al., 1998; Poncer et al., 2002; Luthi et al., 2004). However, a recent study demonstrated that GluR1-S831 mediated increase in single channel conductance is absent when GluR1 is present with GluR2 in a heteromeric complex (Oh & Derkach, 2005). Since the majority of native AMPA receptors are GluR1/GluR2 heteromers (Wenthold et al., 1996), GluR1-S831 phosphorylation dependent increase in channel conductance likely plays a relatively minor role. This may explain the neuron-to-neuron variability in observing increases in AMPA receptor conductance following LTP (Benke et al., 1998; Luthi et al., 2004). In any case, this exemplifies the importance of potential interaction between different subunits in regulating AMPA receptor function, and that even the same phosphorylation site can affect GluR1-containing AMPA receptors differently depending on whether they are assembled in homomeric or heteromeric complexes. It is unlikely that GluR1-S831 is involved in LTP by regulating synaptic insertion of AMPA receptors, because GluR1 lacking S831 phosphorylation site (S831A mutation) was still able to insert into synapses in a CaMKII-dependent manner (Hayashi et al., 2000). This suggests that CaMKII may act on other PSD proteins to mediate the synaptic insertion of GluR1 containing AMPA receptors following LTP. One potential candidate PSD protein is synapse associated protein 97 (SAP97) as will be discussed later (see Section 9.1).

Initial reports on the involvement of GluR1-S845 in synaptic plasticity showed that dephosphorylation of this residue is associated with LTD (Kameyama et al., 1998; Lee et al., 1998, 2000), and also necessary for induction of LTD (Lee et al., 2003). More recently, phosphorylation of GluR1-S845 was shown to be critical for activity-dependent insertion of AMPA receptors following LTP (Esteban et al., 2003), which may be via increasing

extrasynaptic pool of GluR1 (Oh et al., 2006). Therefore, reversible regulation of GluR1-S845 seems to be involved in mediating bidirectional synaptic plasticity. Basal phosphorylation of GluR1-S845 at synapses seems to rely on A-kinase anchoring protein 79/150 (AKAP79/150) (Tavalin et al., 2002), which brings PKA in close proximity to the receptors by binding to a GluR1 interacting molecule SAP97 (Colledge et al., 2000). In accordance with this, disrupting PKA binding to AKAP79/150 produces a rundown of AMPA receptor current (Rosenmund et al., 1994; Snyder et al., 2005), and occludes further LTD induction (Snyder et al., 2005). A recent study demonstrated that LTD induction dissociates AKAP79/150 from AMPA receptor complex (Smith et al., 2006), which could further favor dephosphorylation of GluR1-S845.

The mechanisms by which dephosphorylation of GluR1-S845 mediates LTD is likely through affecting AMPA receptor endocytosis. In support of this idea, dephosphorylation of GluR1-S845 has been associated with AMPA receptor internalization following LTD (Lee et al., 2003; Brown et al., 2005). Whether GluR1-S845 dephosphorylation is transient or persistent seems to determine if the internalized AMPA receptors will recycle back to the plasma membrane or trafficked to lysosome for degradation, respectively (Ehlers, 2000). In line with this, LTD is associated with a persistent dephosphorylation of GluR1-S845 (Lee et al., 1998, 2000) and a reduction in synaptic AMPA receptor amount (Heynen et al., 2000), which could be due to degradation of the internalized receptors. Endocytosis of AMPA receptors following LTD has also been shown to rely on GluR2 subunit, suggesting a potential interaction between these 2 subunits in regulating LTD expression (see Section 8.2 for further discussions).

Recently several additional phosphorylation sites on GluR1 have been identified and characterized (Lee et al., 2002; Boehm et al., 2006). Among these, GluR1-S818 seems like an additional regulatory site for synaptic plasticity. Preliminary results showed that this site is phosphorylated by PKC and increased by LTP (Boehm et al., 2006). In addition, increasing phosphorylation by PKC or a mutation that mimics phosphorylation of S818 drives GluR1 into synapses, while a mutation that prevents phosphorylation blocks LTP (Boehm et al., 2006).

8.2. Phosphorylation of GluR2 subunit

GluR2 is a key subunit, which renders the AMPA receptor channel impermeable to Ca^{2+} and confers specific biophysical properties (reviewed in Tanaka et al., 2000). There are several serine phosphorylation sites (S863 and S880) mapped on the intracellular carboxy-terminal of GluR2 that are phosphorylated by PKC (Matsuda et al., 1999; Chung et al., 2000; McDonald et al., 2001; Table 3). Among these, serine-880 has been implicated to play a role in synaptic plasticity. GluR2-S880 is part of the extreme carboxy-terminal PDZ ligand sequence ($SVKI_{COOH}$), which binds 2 groups of PDZ proteins depending on its phosphorylation state. When unphosphorylated at S880, GluR2 can interact with PDZ domains of glutamate receptor interacting protein (GRIP)/ABP (AMPA receptor binding protein) or protein interacting with C-kinase-1 (PICK-1) (Matsuda et al., 1999; Chung et al., 2000). On the other hand, phosphorylated S880 allows preferential binding to PICK-1 (Matsuda et al., 1999; Chung et al., 2000). Interaction between GluR2 and GRIP family of proteins has been shown to stabilize AMPA receptors at synaptic locations (Dong et al., 1997; Srivastava et al., 1998; Wyszynski et al., 1999; Osten et al., 2000) or intracellular pools (Daw et al., 2000; Braithwaite et al., 2002). On the other hand, interaction of S880 phosphorylated GluR2 to PICK-1 has been demonstrated to either promote endocytosis of the receptors (Chung et al., 2000; Iwakura et al., 2001; Perez et al., 2001; Terashima et al., 2004; Lu and Ziff, 2005) or allow trafficking of receptors to the plasma membrane (Daw et al., 2000; Gardner et al., 2005). Therefore, regulation of the GluR2-S880 phosphorylation site can critically change the function of AMPA receptors by altering its interaction with GRIP and PICK-1.

There is evidence suggesting that GluR2-S880 phosphorylation is critical for LTD expression in hippocampal CA1 pyramidal neurons. Postsynaptic injection of phospho-peptides (or

peptides that mimic S880 phosphorylation) that can compete with GluR2 in binding with PICK-1 prevents LTD expression, while injecting non-phosphopeptides that will predominantly disrupt interaction with GRIP does not (Kim et al., 2001; Seidenman et al., 2003; but see Daw et al., 2000). In addition, transfection of mutant GluR2 subunits that mimic phosphorylation of S880 produces synaptic depression that occludes further LTD expression, while transfection of mutant GluR2 subunits that prevents S880 phosphorylation blocks LTD (Seidenman et al., 2003).

However, it is unclear at this moment how a GluR2-S880 mediated endocytosis mechanism acts with GluR1-S845 dephosphorylation dependent mechanism to express LTD. Since both mechanisms seem to be necessary for LTD expression, it is likely that they act sequentially to mediate LTD. One possibility is that LTD induction triggers AMPA receptor endocytosis by a GluR2-dependent mechanism, and a subsequent dephosphorylation of GluR1 subunit may occur to prevent the receptors from recycling back to synapses. On the other hand, LTD induction may first trigger dephosphorylation of GluR1, which may then acts to unleash the GluR2-mediated endocytosis mechanism to express LTD (for a more detailed discussion see Lee, 2006).

GluR2 is also phosphorylated on a tyrosine residue (Y842) by Src (Hayashi & Huganir, 2004). Src-induced phosphorylation of GluR2-Y842 causes a decrease in GRIP binding, while not affecting PICK-1 interaction with GluR2 (Hayashi & Huganir, 2004). This implies that GluR2-Y842 phosphorylation should also play a role in GluR2 internalization, similar to GluR2-S880. In accordance, a mutation that prevents phosphorylation of Y842, blocks AMPA- and NMDA-induced internalization of GluR2 (Hayashi & Huganir, 2004). These results underscore the importance of crosstalk between serine/threonine protein kinase systems and tyrosine phosphorylation signaling in regulating AMPA receptor mediated synaptic plasticity.

8.3. Phosphorylation of GluR3 and GluR4 subunits

GluR3 and GluR4 are not as highly expressed in the adult forebrain structures as compared to GluR1 and GluR2 subunits (Petralia & Wenthold, 1992; Martin et al., 1993). However, they do contain homologous phosphorylation sites corresponding to those on GluR1 and GluR2, which have been implicated in synaptic plasticity mechanisms (reviewed in Song & Huganir, 2002). The intracellular carboxy-domain of GluR3 displays sequence homology to GluR2, including a phosphorylation site on the extreme C-tail PDZ ligand region. Since the PDZ ligand of GluR3 is the same sequence as that of GluR2, it suggests that phosphorylation of GluR3 may also allow regulate its interaction with PDZ proteins. However, there is no direct demonstration of the involvement of GluR3 phosphorylation in synaptic plasticity.

Expression of GluR4 in the hippocampus is limited during early postnatal period of development (Zhu et al., 2000; for contradictory results, see Kolleker et al., 2003), and can be inserted into synapses by spontaneous activity (Zhu et al., 2000). Intracellular domain of GluR4 subunits shows some homology to GluR1, and several phosphorylation sites have been mapped to this region, some of which are equivalent to GluR1 phosphorylation sites discussed previously. GluR4-S842 is phosphorylated by PKA in vivo (Carvalho et al., 1999), while T830 has been identified as a PKC target (Carvalho et al., 1999; Table 3). In the hippocampus, PKA activity was shown to insert GluR4 homomeric receptors to synapses that is dependent on S842 (Esteban et al., 2003).

If GluR4-dependent mechanisms are dominant during early development, it suggests that the LTP mechanism changes as the animals mature. This is consistent with reports demonstrating that signaling pathways involved in LTP indeed changes during development (Wikstrom et al., 2003; Yasuda et al., 2003; Palmer et al., 2004). Especially, the observation that LTP is PKA-dependent, but CaMKII-independent, at early postnatal ages (Wikstrom et al., 2003; Yasuda

et al., 2003) supports the role of PKA-dependent GluR4 phosphorylation in mediating LTP during the early developmental period. Taken together with the findings that GluR1 knockout mice or GluR1 phosphorylation site mutants show normal LTP when young (Jensen et al., 2003; Lee et al., 2003), these results suggest that the LTP mechanism changes from a PKA-GluR4 dependent mechanism to a CaMKII-GluR1 dependent mechanism during development.

9. Glutamate receptor associated phosphoproteins in the postsynaptic density

9.1. Synapse associated protein 97

SAP97 is a member of the membrane-associated guanylate kinase (MAGUK) protein family, which act as scaffolding proteins for organizing postsynaptic molecules, including ionotropic glutamate receptors. Similar to other members of the MAGUK proteins, SAP97 has 3 PDZ domains, 1 Src homology domain (SH3) domain, and a guanylate kinase (GK) domain. The PDZ domains of SAP97 interact with the extreme GluR1 carboxy-tail, which has a type I PDZ ligand motif (-TGL_{COOH}) (Leonard et al., 1998; Colledge et al., 2000; Cai et al., 2002), and the carboxy-tail of NR2A, which also has a PDZ ligand motif (-SDV_{COOH}) (Bassand et al., 1999; Gardoni et al., 2003). SAP97 is known to interact mainly with the intracellular population of AMPA receptors present in the early biosynthetic pathways (Sans et al., 2001), however, it is also co-localized at postsynaptic loci together with GluR1 (Valtschanoff et al., 2000).

Two CaMKII phosphorylation sites have been mapped on SAP97: one is serine-39, which is located on the N-terminal L27 domain (Mauceri et al., 2004), and the other is serine-232 within the PDZ1 domain (Gardoni et al., 2003). Despite being phosphorylated by the same enzyme, these 2 sites seem to mediate different functions. Phosphorylation of serine-39 residue is necessary and sufficient to traffic SAP97 into spines, as well as for trafficking GluR1 subunit to spines (Mauceri et al., 2004). These data are consistent with a role of SAP97 in mediating LTP. A current hypothesis for LTP expression put forth by Lisman proposed SAP97 to be a member of an “AMPA channel anchoring assembly”, which is a protein complex that mediates insertion of AMPA receptors to synapses in a CaMKII-dependent fashion (Lisman et al., 2002). SAP97 fits nicely to this role, since it can bind GluR1 subunit of AMPA receptors and deliver them to spines upon phosphorylation of serine-39 by CaMKII.

In addition to trafficking AMPA receptors to synapses, CaMKII phosphorylation of SAP97 can regulate NMDA receptors via phosphorylation of serine-232. CaMKII phosphorylation of this site disrupts the interaction of SAP97 with NR2A subunit without affecting its interaction with AMPA receptor GluR1 subunit (Gardoni et al., 2003). This is thought to be a mechanism to release NR2A from SAP97 upon delivery to the PSD, where CaMKII may be highly active (Gardoni et al., 2003). If this is a mechanism for activity-dependent delivery of NR2A to synapses, this could be involved in “sliding threshold” type of metaplasticity, where an activity-dependent switch from NR2B to NR2A has been proposed to slide the threshold to prevent further LTP induction (Quinlan, Olstein et al., 1999; Quinlan, Philpot et al., 1999; Philpot et al., 2001). Whether the 2 CaMKII phosphorylation sites on SAP97 work in harmony or are mutually exclusive in regulating function is currently unknown.

9.2. Stargazin

Stargazin is a member of transmembrane AMPA receptor regulatory proteins (TARP), which interact with AMPA receptors (Tomita et al., 2003). Recent structural analysis of native AMPA receptors reveal stargazin as an integral part of the AMPA receptor channel (Fukata et al., 2005; Nakagawa et al., 2005; Nicoll et al., 2006). Assembly of stargazin with AMPA receptors greatly enhances current flow through the channel (Priel et al., 2005; Tomita et al., 2005). Moreover, a line of mice lacking stargazin by a spontaneous mutation (called “stargazer” mice) lack

functional AMPA receptors in the cerebellum (Hashimoto et al., 1999; Chen et al., 2000), which correlates with motor deficits (i.e. ataxia) (reviewed in Letts, 2005; Nicoll et al., 2006). In the forebrain structures, other stargazin related TARPs are thought to be involved in regulating AMPA receptor function. For example, gamma-3 is highly expressed in the cortex, while gamma-8 is almost exclusively expressed in the hippocampus (Tomita et al., 2003).

Stargazin has a PDZ ligand region (-TTPV$_{COOH}$) that interacts with PSD95 (Chen et al., 2000). A mutant stargazin lacking the PDZ ligand is able to traffic AMPA receptors to plasma membrane, but fails to incorporate them into synapses (Chen et al., 2000). Similar results were seen in hippocampal neurons of a knockout mouse lacking TARP gamma-8 (Rouach et al., 2005). Moreover a direct interaction of stargazin with PSD95 is necessary for increasing synaptic AMPA receptor content (Schnell et al., 2002). Therefore, TARPs seem to mediate AMPA receptor trafficking by 2 separate means: first, by bringing the receptors to the plasma membrane, which does not require its interaction with PSD95, and second is by localizing the surface receptors to synapses by binding to PSD95.

Recent studies demonstrated that stargazin can be phosphorylated (Chetkovich et al., 2002; Choi et al., 2002; Tomita et al., 2005). Phosphorylation of stargazin by PKA occurs on Threonine-321, which prevents PSD95 binding (Chetkovich et al., 2002; Choi et al., 2002). This predicts that PKA phosphorylation of stargazin would disrupt AMPA receptor synaptic localization, which is consistent with the observation that a mutation mimicking T321 phosphorylation decreases AMPA receptor-mediated synaptic current (Chetkovich et al., 2002). On the other hand, phosphorylation of several conserved serine residues on the cytoplasmic domain of TARP enhances synaptic trafficking of AMPA receptors without affecting surface delivery of these receptors (Tomita et al., 2005). Phosphorylation of these serine residues is high under basal conditions, and their regulation is critical for LTP and LTD (Tomita et al., 2005). Phosphorylation of these conserved serine residues is likely mediated by PKC and CaMKII, while dephosphorylation depends on PP1 and PP2B activity (Tomita et al., 2005).

10. Concluding remarks

Phosphorylation is a major mechanism to rapidly and reversibly regulate function of a vast number of cellular proteins. Neurons are no exception, and many of the synaptic proteins, both pre- and post-synaptic, are phosphoproteins. Regulation of these phosphoproteins is likely important for synaptic function and plasticity. Regulation of various protein kinases and protein phosphatases by neuronal activity allows for coordinated control of synaptic phosphoproteins. However, we are far from an understanding of how the orchestrated changes in the activity of diverse protein kinases and protein phosphatases translate into the proper regulation of synaptic proteins that is required to mediate specific changes in synaptic function. Many of the challenges in our understanding are due to the fact that signaling pathways crosstalk with each other, which adds another level of complexity. Also, the signaling pathways recruited by neural activity seem to depend on the pattern of synaptic activity, presence of various neuromodulators, and on the prior history of synaptic activity. Despite the complexity of signaling pathways involved, our understanding of the downstream effectors might provide us with guide lights in which we can begin to explore the exquisite regulation of synaptic function by neural activity.

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References

Abel T, Nguyen PV, Barad M, Deuel TA, Kandel ER, Bourtchouladze R. Genetic demonstration of a role for PKA in the late phase of LTP and in hippocampus-based long-term memory. Cell 1997;88:615–626. [PubMed: 9054501]

Abeliovich A, Chen C, Goda Y, Silva AJ, Stevens CF, Tonegawa S. Modified hippocampal long-term potentiation in PKC gamma-mutant mice. Cell 1993;75:1253–1262. [PubMed: 8269509]

Abraham WC, Bear MF. Metaplasticity: the plasticity of synaptic plasticity. Trends Neurosci 1996;19:126–130. [PubMed: 8658594]

Ahmed T, Frey JU. Plasticity-specific phosphorylation of CaMKII, MAP-kinases and CREB during late-LTP in rat hippocampal slices in vitro. Neuropharmacology 2005;49:477–492. [PubMed: 16005911]

Akers RF, Routtenberg A. Protein kinase C phosphorylates a 47 Mr protein (F1) directly related to synaptic plasticity. Brain Res 1985;334:147–151. [PubMed: 3158377]

Akers RF, Lovinger DM, Colley PA, Linden DJ, Routtenberg A. Translocation of protein kinase C activity may mediate hippocampal long-term potentiation. Science 1986;231:587–589. [PubMed: 3003904]

Aloyo VJ, Zwiers H, Gispen WH. Phosphorylation of B-50 protein by calcium-activated, phospholipid-dependent protein kinase and B-50 protein kinase. J Neurochem 1983;41:649–653. [PubMed: 6308167]

Apel ED, Litchfield DW, Clark RH, Krebs EG, Storm DR. Phosphorylation of neuromodulin (GAP-43) by casein kinase II. Identification of phosphorylation sites and regulation by calmodulin. J Biol Chem 1991;266:10544–10551. [PubMed: 1828073]

Banke TG, Bowie D, Lee H, Huganir RL, Schousboe A, Traynelis SF. Control of GluR1 AMPA receptor function by cAMP-dependent protein kinase. J Neurosci 2000;20:89–102. [PubMed: 10627585]

Barria A, Malinow R. Subunit-specific NMDA receptor trafficking to synapses. Neuron 2002;35:345–353. [PubMed: 12160751]

Barria A, Malinow R. NMDA receptor subunit composition controls synaptic plasticity by regulating binding to CaMKII. Neuron 2005;48:289–301. [PubMed: 16242409]

Barria A, Derkach V, Soderling T. Identification of the Ca^{2+}/calmodulin-dependent protein kinase II regulatory phosphorylation site in the alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate-type glutamate receptor. J Biol Chem 1997;272:32727–32730. [PubMed: 9407043]

Barria A, Muller D, Derkach V, Griffith LC, Soderling TR. Regulatory phosphorylation of AMPA-type glutamate receptors by CaMKII during long-term potentiation. Science 1997;276:2042–2045. [PubMed: 9197267]

Bassand P, Bernard A, Rafiki A, Gayet D, Khrestchatisky M. Differential interaction of the tSXV motifs of the NR1 and NR2A NMDA receptor subunits with PSD95 and SAP97. Eur J Neurosci 1999;11:2031–2043. [PubMed: 10336672]

Baudier J, Bronner C, Kligman D, Cole RD. Protein kinase C substrates from bovine brain. Purification and characterization of neuromodulin, a neuron-specific calmodulin-binding protein. J Biol Chem 1989;264:1824–1828. [PubMed: 2521487]

Bayer KU, Lohler J, Schulman H, Harbers K. Developmental expression of the CaM kinase II isoforms: ubiquitous gamma- and delta-CaM kinase II are the early isoforms and most abundant in the developing nervous system. Brain Res Mol Brain Res 1999;70:147–154. [PubMed: 10381553]

Bayer KU, De Koninck P, Leonard AS, Hell JW, Schulman H. Interaction with the NMDA receptor locks CaMKII in an active conformation. Nature 2001;411:801–805. [PubMed: 11459059]

Bayer KU, LeBel E, McDonald GL, O'Leary H, Schulman H, De Koninck P. Transition from reversible to persistent binding of CaMKII to postsynaptic sites and NR2B. J Neurosci 2006;26:1164–1174. [PubMed: 16436603]

Bear MF. Mechanism for a sliding synaptic modification threshold. Neuron 1995;15:1–4. [PubMed: 7619513]

Bear MF, Cooper LN, Ebner FF. A physiological basis for a theory of synapse modification. Science 1987;237:42–48. [PubMed: 3037696]

Bejar R, Yasuda R, Krugers H, Hood K, Mayford M. Transgenic calmodulin-dependent protein kinase II activation: dose-dependent effects on synaptic plasticity, learning, and memory. J Neurosci 2002;22:5719–5726. [PubMed: 12097524]

Ben-Ari Y, Aniksztejn L, Bregestovski P. Protein kinase C modulation of NMDA currents: an important link for LTP induction. Trends Neurosci 1992;15:333–339. [PubMed: 1382331]

Benke TA, Luthi A, Isaac JT, Collingridge GL. Modulation of AMPA receptor unitary conductance by synaptic activity. Nature 1998;393:793–797. [PubMed: 9655394]

Berberich S, Punnakkal P, Jensen V, Pawlak V, Seeburg PH, Hvalby O, et al. Lack of NMDA receptor subtype selectivity for hippocampal long-term potentiation. J Neurosci 2005;25:6907–6910. [PubMed: 16033900]

Bienenstock EL, Cooper LN, Munro PW. Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. J Neurosci 1982a;2:32–48. [PubMed: 7054394]

Bienenstock EL, Cooper LN, Munro PW. Theory for the development of neuron selectivity: Orientation specificity and binocular interaction in visual cortex. J Neurosci 1982b;2:32–48. [PubMed: 7054394]

Blackstone C, Murphy TH, Moss SJ, Baraban JM, Huganir RL. Cyclic AMP and synaptic activity-dependent phosphorylation of AMPA-preferring glutamate receptors. J Neurosci 1994;14:7585–7593. [PubMed: 7527845]

Blanquet PR. Casein kinase 2 as a potentially important enzyme in the nervous system. Prog Neurobiol 2000;60:211–246. [PubMed: 10658642]

Bliss TV, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 1973;232:331–356. [PubMed: 4727084]

Blitzer RD, Wong T, Nouranifar R, Iyengar R, Landau EM. Postsynaptic cAMP pathway gates early LTP in hippocampal CA1 region. Neuron 1995;15:1403–1414. [PubMed: 8845163]

Blitzer RD, Connor JH, Brown GP, Wong T, Shenolikar S, Iyengar R, et al. Gating of CaMKII by cAMP-regulated protein phosphatase activity during LTP. Science 1998;280:1940–1942. [PubMed: 9632393]

Boehm J, Kang MG, Johnson RC, Esteban J, Huganir RL, Malinow R. Synaptic incorportation of AMPA receptors during LTP is controlled by a PKC phosphorylation site on GluR1. Neuron 2006;51:213–225. [PubMed: 16846856]

Bonifacino JS, Traub LM. Signals for sorting of transmembrane proteins to endosomes and lysosomes. Annu Rev Biochem 2003;72:395–447. [PubMed: 12651740]

Boulanger LM, Lombroso PJ, Raghunathan A, During MJ, Wahle P, Naegele JR. Cellular and molecular characterization of a brain-enriched protein tyrosine phosphatase. J Neurosci 1995;15:1532–1544. [PubMed: 7869116]

Boulter J, Hollmann M, O'Shea-Greenfield A, Hartley M, Deneris E, Maron C, et al. Molecular cloning and functional expression of glutamate receptor subunit genes. Science 1990;249:1033–1037. [PubMed: 2168579]

Bowie D, Mayer ML. Inward rectification of both AMPA and kainate subtype glutamate receptors generated by polyamine-mediated ion channel block. Neuron 1995;15:453–462. [PubMed: 7646897]

Braithwaite SP, Xia H, Malenka RC. Differential roles for NSF and GRIP/ABP in AMPA receptor cycling. Proc Natl Acad Sci U S A 2002;99:7096–7101. [PubMed: 12011465]

Brandon EP, Zhuo M, Huang YY, Qi M, Gerhold KA, Burton KA, et al. Hippocampal long-term depression and depotentiation are defective in mice carrying a targeted disruption of the gene encoding the RI beta subunit of cAMP-dependent protein kinase. Proc Natl Acad Sci U S A 1995;92:8851–8855. [PubMed: 7568030]

Brandon EP, Idzerda RL, McKnight GS. PKA isoforms, neural pathways, and behaviour: making the connection. Curr Opin Neurobiol 1997;7:397–403. [PubMed: 9232801]

Brocke L, Chiang LW, Wagner PD, Schulman H. Functional implications of the subunit composition of neuronal CaM kinase II. J Biol Chem 1999;274:22713–22722. [PubMed: 10428854]

Brown GP, Blitzer RD, Connor JH, Wong T, Shenolikar S, Iyengar R, et al. Long-term potentiation induced by theta frequency stimulation is regulated by a protein phosphatase-1-operated gate. J Neurosci 2000;20:7880–7887. [PubMed: 11050107]

Brown TC, Tran IC, Backos DS, Esteban JA. NMDA receptor-dependent activation of the small GTPase Rab5 drives the removal of synaptic AMPA receptors during hippocampal LTD. Neuron 2005;45:81–94. [PubMed: 15629704]

Burrone J, O'Byrne M, Murthy VN. Multiple forms of synaptic plasticity triggered by selective suppression of activity in individual neurons. Nature 2002;420:414–418. [PubMed: 12459783]

Cai C, Coleman SK, Niemi K, Keinanen K. Selective binding of synapse-associated protein 97 to GluR-A alpha-amino-5-hydroxy-3-methyl-4-isoxazole propionate receptor subunit is determined by a novel sequence motif. J Biol Chem 2002;277:31484–31490. [PubMed: 12070168]

Carvalho AL, Kameyama K, Huganir RL. Characterization of phosphorylation sites on the glutamate receptor 4 subunit of the AMPA receptors. J Neurosci 1999;19:4748–4754. [PubMed: 10366608]

Chakravarthy B, Morley P, Whitfield J. Ca^{2+}-calmodulin and protein kinase Cs: a hypothetical synthesis of their conflicting convergences on shared substrate domains. Trends Neurosci 1999;22:12–16. [PubMed: 10088994]

Charriaut-Marlangue C, Otani S, Creuzet C, Ben-Ari Y, Loeb J. Rapid activation of hippocampal casein kinase II during long-term potentiation. Proc Natl Acad Sci U S A 1991;88:10232–10236. [PubMed: 1946443]

Chen SJ, Sweatt JD, Klann E. Enhanced phosphorylation of the postsynaptic protein kinase C substrate RC3/neurogranin during long-term potentiation. Brain Res 1997;749:181–187. [PubMed: 9138717]

Chen L, Chetkovich DM, Petralia RS, Sweeney NT, Kawasaki Y, Wenthold RJ, et al. Stargazin regulates synaptic targeting of AMPA receptors by two distinct mechanisms. Nature 2000;408:936–943. [PubMed: 11140673]

Chetkovich DM, Chen L, Stocker TJ, Nicoll RA, Bredt DS. Phosphorylation of the postsynaptic density-95 (PSD95)/discs large/zona occludens-1 binding site of stargazin regulates binding to PSD95 and synaptic targeting of AMPA receptors. J Neurosci 2002;22:5791–5796. [PubMed: 12122038]

Choi J, Ko J, Park E, Lee JR, Yoon J, Lim S, et al. Phosphorylation of stargazin by protein kinase A regulates its interaction with PSD95. J Biol Chem 2002;277:12359–12363. [PubMed: 11805122]

Chung HJ, Huang YH, Lau LF, Huganir RL. Regulation of the NMDA receptor complex and trafficking by activity-dependent phosphorylation of the NR2B subunit PDZ ligand. J Neurosci 2004;24:10248–10259. [PubMed: 15537897]

Chung HJ, Xia J, Scannevin RH, Zhang X, Huganir RL. Phosphorylation of the AMPA receptor subunit GluR2 differentially regulates its interaction with PDZ domain-containing proteins. J Neurosci 2000;20:7258–7267. [PubMed: 11007883]

Clark KA, Collingridge GL. Synaptic potentiation of dual-component excitatory postsynaptic currents in the rat hippocampus. J Physiol 1995;482(Pt 1):39–52. [PubMed: 7730988]

Clem RL, Barth A. Pathway-specific trafficking of native AMPARs by in vivo experience. Neuron 2006;49:663–670. [PubMed: 16504942]

Cohen AS, Abraham WC. Facilitation of long-term potentiation by prior activation of metabotropic glutamate receptors. J Neurophysiol 1996;76:953–962. [PubMed: 8871210]

Cohen AS, Raymond CR, Abraham WC. Priming of long-term potentiation induced by activation of metabotropic glutamate receptors coupled to phospholipase C. Hippocampus 1998;8:160–170. [PubMed: 9572722]

Colbran RJ. Inactivation of Ca^{2+}/calmodulin-dependent protein kinase II by basal autophosphorylation. J Biol Chem 1993;268:7163–7170. [PubMed: 8385100]

Colbran RJ, Brown AM. Calcium/calmodulin-dependent protein kinase II and synaptic plasticity. Curr Opin Neurobiol 2004;14:318–327. [PubMed: 15194112]

Colledge M, Dean RA, Scott GK, Langeberg LK, Huganir RL, Scott JD. Targeting of PKA to glutamate receptors through a MAGUK–AKAP complex. Neuron 2000;27:107–119. [PubMed: 10939335]

Collins MO, Yu L, Coba MP, Husi H, Campuzano I, Blackstock WP, et al. Proteomic analysis of in vivo phosphorylated synaptic proteins. J Biol Chem 2005;280:5972–5982. [PubMed: 15572359]

Correia SS, Duarte CB, Faro CJ, Pires EV, Carvalho AL. Protein kinase C gamma associates directly with the GluR4 alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor subunit. Effect on receptor phosphorylation. J Biol Chem 2003;278:6307–6313. [PubMed: 12471040]

Coussens CM, Williams JM, Ireland DR, Abraham WC. Tyrosine phosphorylation-dependent inhibition of hippocampal synaptic plasticity. Neuropharmacology 2000;39:2267–2277. [PubMed: 10974310]

Cull-Candy S, Brickley S, Farrant M. NMDA receptor subunits: diversity, development and disease. Curr Opin Neurobiol 2001;11:327–335. [PubMed: 11399431]

Cummings JA, Mulkey RM, Nicoll RA, Malenka RC. Ca^{2+} signaling requirements for long-term depression in the hippocampus. Neuron 1996;16:825–833. [PubMed: 8608000]

Czernik AJ, Pang DT, Greengard P. Amino acid sequences surrounding the cAMP-dependent and calcium/calmodulin-dependent phosphorylation sites in rat and bovine synapsin I. Proc Natl Acad Sci U S A 1987;84:7518–7522. [PubMed: 3118371]

Dan Y, Poo MM. Spike timing-dependent plasticity of neural circuits. Neuron 2004;44:23–30. [PubMed: 15450157]

Daw MI, Chittajallu R, Bortolotto ZA, Dev KK, Duprat F, Henley JM, et al. PDZ proteins interacting with C-terminal GluR2/3 are involved in a PKC-dependent regulation of AMPA receptors at hippocampal synapses. Neuron 2000;28:873–886. [PubMed: 11163273]

De Koninck P, Schulman H. Sensitivity of CaM kinase II to the frequency of Ca^{2+} oscillations. Science 1998;279:227–230. [PubMed: 9422695]

Deloulme JC, Sensenbrenner M, Baudier J. A rapid purification method for neurogranin, a brain specific calmodulin-binding protein kinase C substrate. FEBS Lett 1991;282:183–188. [PubMed: 2026258]

Derkach V, Barria A, Soderling TR. Ca^{2+}/calmodulin-kinase II enhances channel conductance of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate type glutamate receptors. Proc Natl Acad Sci U S A 1999;96:3269–3274. [PubMed: 10077673]

Donevan SD, Rogawski MA. Intracellular polyamines mediate inward rectification of Ca($^{2+}$)-permeable alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. Proc Natl Acad Sci U S A 1995;92:9298–9302. [PubMed: 7568121]

Dong H, O'Brien RJ, Fung ET, Lanahan AA, Worley PF, Huganir RL. GRIP: a synaptic PDZ domain-containing protein that interacts with AMPA receptors. Nature 1997;386:279–284. [PubMed: 9069286]

Dudek SM, Bear MF. Homosynaptic long-term depression in area CA1 of hippocampus and effects of *N*-methyl-d-aspartate receptor blockade. Proc Natl Acad Sci U S A 1992;89:4363–4367. [PubMed: 1350090]

Ehlers MD. Reinsertion or degradation of AMPA receptors determined by activity-dependent endocytic sorting. Neuron 2000;28:511–525. [PubMed: 11144360]

Ehlers MD, Tingley WG, Huganir RL. Regulated subcellular distribution of the NR1 subunit of the NMDA receptor. Science 1995;269:1734–1737. [PubMed: 7569904]

Elgersma Y, Fedorov NB, Ikonen S, Choi ES, Elgersma M, Carvalho OM, et al. Inhibitory autophosphorylation of CaMKII controls PSD association, plasticity, and learning. Neuron 2002;36:493–505. [PubMed: 12408851]

English JD, Sweatt JD. Activation of p42 mitogen-activated protein kinase in hippocampal long term potentiation. J Biol Chem 1996;271:24329–24332. [PubMed: 8798683]

English JD, Sweatt JD. A requirement for the mitogen-activated protein kinase cascade in hippocampal long term potentiation. J Biol Chem 1997;272:19103–19106. [PubMed: 9235897]

Esteban JA, Shi SH, Wilson C, Nuriya M, Huganir RL, Malinow R. PKA phosphorylation of AMPA receptor subunits controls synaptic trafficking underlying plasticity. Nat Neurosci 2003;6:136–143. [PubMed: 12536214]

Feil R, Hofmann F, Kleppisch T. Function of cGMP-dependent protein kinases in the nervous system. Rev Neurosci 2005;16:23–41. [PubMed: 15810652]

Fink CC, Meyer T. Molecular mechanisms of CaMKII activation in neuronal plasticity. Curr Opin Neurobiol 2002;12:293–299. [PubMed: 12049936]

Fink CC, Bayer KU, Myers JW, Ferrell JE Jr, Schulman H, Meyer T. Selective regulation of neurite extension and synapse formation by the beta but not the alpha isoform of CaMKII. Neuron 2003;39:283–297. [PubMed: 12873385]

Fong DK, Rao A, Crump FT, Craig AM. Rapid synaptic remodeling by protein kinase C: reciprocal translocation of NMDA receptors and calcium/calmodulin-dependent kinase II. J Neurosci 2002;22:2153–2164. [PubMed: 11896155]

Frankland PW, O'Brien C, Ohno M, Kirkwood A, Silva AJ. Alpha-CaMKII-dependent plasticity in the cortex is required for permanent memory. Nature 2001;411:309–313. [PubMed: 11357133]

Froemke RC, Poo MM, Dan Y. Spike-timing-dependent synaptic plasticity depends on dendritic location. Nature 2005;434:221–225. [PubMed: 15759002]

Fujii S, Saito K, Miyakawa H, Ito K, Kato H. Reversal of long-term potentiation (depotentiation) induced by tetanus stimulation of the input to CA1 neurons of guinea pig hippocampal slices. Brain Res 1991;555:112–122. [PubMed: 1681992]

Fukata Y, Tzingounis AV, Trinidad JC, Fukata M, Burlingame AL, Nicoll RA, et al. Molecular constituents of neuronal AMPA receptors. J Cell Biol 2005;169:399–404. [PubMed: 15883194]

Fukunaga K, Stoppini L, Miyamoto E, Muller D. Long-term potentiation is associated with an increased activity of Ca^{2+}/calmodulin-dependent protein kinase II. J Biol Chem 1993;268:7863–7867. [PubMed: 8385124]

Fukunaga K, Muller D, Miyamoto E. Increased phosphorylation of Ca^{2+}/calmodulin-dependent protein kinase II and its endogenous substrates in the induction of long-term potentiation. J Biol Chem 1995;270:6119–6124. [PubMed: 7890745]

Fukunaga K, Muller D, Ohmitsu M, Bako E, DePaoli-Roach AA, Miyamoto E. Decreased protein phosphatase 2A activity in hippocampal long-term potentiation. J Neurochem 2000;74:807–817. [PubMed: 10646534]

Fykse EM, Li C, Sudhof TC. Phosphorylation of rabphilin-3A by Ca^{2+}/calmodulin- and cAMP-dependent protein kinases in vitro. J Neurosci 1995;15:2385–2395. [PubMed: 7891174]

Gardner SM, Takamiya K, Xia J, Suh JG, Johnson R, Yu S, et al. Calcium-permeable AMPA receptor plasticity is mediated by subunit-specific interactions with PICK1 and NSF. Neuron 2005;45:903–915. [PubMed: 15797551]

Gardoni F, Schrama LH, van Dalen JJ, Gispen WH, Cattabeni F, Di Luca M. AlphaCaMKII binding to the C-terminal tail of NMDA receptor subunit NR2A and its modulation by autophosphorylation. FEBS Lett 1999;456:394–398. [PubMed: 10462051]

Gardoni F, Bellone C, Cattabeni F, Di Luca M. Protein kinase C activation modulates alpha-calmodulin kinase II binding to NR2A subunit of *N*-methyl-d-aspartate receptor complex. J Biol Chem 2001;276:7609–7613. [PubMed: 11104776]

Gardoni F, Mauceri D, Fiorentini C, Bellone C, Missale C, Cattabeni F, et al. CaMKII-dependent phosphorylation regulates SAP97/NR2A interaction. J Biol Chem 2003;278:44745–44752. [PubMed: 12933808]

Gerendasy DD, Herron SR, Jennings PA, Sutcliffe JG. Calmodulin stabilizes an amphiphilic alpha-helix within RC3/neurogranin and GAP-43/neuromodulin only when Ca^{2+} is absent. J Biol Chem 1995;270:6741–6750. [PubMed: 7896819]

Giese KP, Fedorov NB, Filipkowski RK, Silva AJ. Autophosphorylation at Thr286 of the alpha calcium-calmodulin kinase II in LTP and learning. Science 1998;279:870–873. [PubMed: 9452388]

Gisabella B, Rowan MJ, Anwyl R. Mechanisms underlying the inhibition of long-term potentiation by preconditioning stimulation in the hippocampus in vitro. Neuroscience 2003;121:297–305. [PubMed: 14521989]

Goel A, Jiang B, Xu LW, Song L, Kirkwood A, Lee HK. Cross-modal regulation of synaptic AMPA receptors in primary sensory cortices by visual experience. Nat Neurosci 2006;9:1001–1003. [PubMed: 16819524]

Grant SG, O'Dell TJ, Karl KA, Stein PL, Soriano P, Kandel ER. Impaired long-term potentiation, spatial learning, and hippocampal development in fyn mutant mice. Science 1992;258:1903–1910. [PubMed: 1361685]

Grosshans DR, Clayton DA, Coultrap SJ, Browning MD. LTP leads to rapid surface expression of NMDA but not AMPA receptors in adult rat CA1. Nat Neurosci 2002;5:27–33. [PubMed: 11740502]

Hardingham N, Glazewski S, Pakhotin P, Mizuno K, Chapman PF, Giese KP, et al. Neocortical long-term potentiation and experience-dependent synaptic plasticity require alpha-calcium/calmodulin-dependent protein kinase II autophosphorylation. J Neurosci 2003;23:4428–4436. [PubMed: 12805283]

Hashimoto Y, Schworer CM, Colbran RJ, Soderling TR. Autophosphorylation of Ca^{2+}/calmodulin-dependent protein kinase II. Effects on total and Ca^{2+}-independent activities and kinetic parameters. J Biol Chem 1987;262:8051–8055. [PubMed: 3110142]

Hashimoto K, Fukaya M, Qiao X, Sakimura K, Watanabe M, Kano M. Impairment of AMPA receptor function in cerebellar granule cells of ataxic mutant mouse stargazer. J Neurosci 1999;19:6027–6036. [PubMed: 10407040]

Hayashi T, Huganir RL. Tyrosine phosphorylation and regulation of the AMPA receptor by SRC family tyrosine kinases. J Neurosci 2004;24:6152–6160. [PubMed: 15240807]

Hayashi Y, Shi SH, Esteban JA, Piccini A, Poncer JC, Malinow R. Driving AMPA receptors into synapses by LTP and CaMKII: requirement for GluR1 and PDZ domain interaction. Science 2000;287:2262–2267. [PubMed: 10731148]

Hebb, DO. Organization of Behavior. New York: John Wiley and Sons; 1949.

Hendricson AW, Miao CL, Lippmann MJ, Morrisett RA. Ifenprodil and ethanol enhance NMDA receptor-dependent long-term depression. J Pharmacol Exp Ther 2002;301:938–944. [PubMed: 12023522]

Herron CE, Lester RA, Coan EJ, Collingridge GL. Frequency-dependent involvement of NMDA receptors in the hippocampus: a novel synaptic mechanism. Nature 1986;322:265–268. [PubMed: 2874493]

Heynen AJ, Quinlan EM, Bae DC, Bear MF. Bidirectional, activity-dependent regulation of glutamate receptors in the adult hippocampus in vivo. Neuron 2000;28:527–536. [PubMed: 11144361]

Hinds HL, Tonegawa S, Malinow R. CA1 long-term potentiation is diminished but present in hippocampal slices from alpha-CaMKII mutant mice. Learn Mem 1998;5:344–354. [PubMed: 10454359]

Hollmann M, Hartley M, Heinemann S. Ca^{2+} permeability of KA-AMPA-gated glutamate receptor channels depends on subunit composition. Science 1991;252:851–853. [PubMed: 1709304]

Hrabetova S, Sacktor TC. Bidirectional regulation of protein kinase M zeta in the maintenance of long-term potentiation and long-term depression. J Neurosci 1996;16:5324–5333. [PubMed: 8757245]

Huang CC, Hsu KS. Protein tyrosine kinase is required for the induction of long-term potentiation in the rat hippocampus. J Physiol 1999;520(Pt 3):783–796. [PubMed: 10545144]

Huang YY, Kandel ER. Recruitment of long-lasting and protein kinase A-dependent long-term potentiation in the CA1 region of hippocampus requires repeated tetanization. Learn Mem 1994;1:74–82. [PubMed: 10467587]

Huang YY, Colley PA, Routtenberg A. Postsynaptic then presynaptic protein kinase C activity may be necessary for long-term potentiation. Neuroscience 1992;49:819–827. [PubMed: 1436483]

Huang Y, Lu W, Ali DW, Pelkey KA, Pitcher GM, Lu YM, et al. CAKbeta/Pyk2 kinase is a signaling link for induction of long-term potentiation in CA1 hippocampus. Neuron 2001;29:485–496. [PubMed: 11239437]

Huang KP, Huang FL, Jager T, Li J, Reymann KG, Balschun D. Neurogranin/RC3 enhances long-term potentiation and learning by promoting calcium-mediated signaling. J Neurosci 2004;24:10660–10669. [PubMed: 15564582]

Husi H, Grant SG. Proteomics of the nervous system. Trends Neurosci 2001;24:259–266. [PubMed: 11311377]

Husi H, Ward MA, Choudhary JS, Blackstock WP, Grant SG. Proteomic analysis of NMDA receptor-adhesion protein signaling complexes. Nat Neurosci 2000;3:661–669. [PubMed: 10862698]

Huttner WB, DeGennaro LJ, Greengard P. Differential phosphorylation of multiple sites in purified protein I by cyclic AMP-dependent and calcium-dependent protein kinases. J Biol Chem 1981;256:1482–1488. [PubMed: 6256398]

Iwakura Y, Nagano T, Kawamura M, Horikawa H, Ibaraki K, Takei N, et al. *N*-methyl-d-aspartate-induced alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptor down-regulation involves interaction of the carboxyl terminus of GluR2/3 with Pick1. Ligand-binding studies using Sindbis vectors carrying AMPA receptor decoys. J Biol Chem 2001;276:40025–40032. [PubMed: 11498531]

Iwamoto T, Yamada Y, Hori K, Watanabe Y, Sobue K, Inui M. Differential modulation of NR1-NR2A and NR1-NR2B subtypes of NMDA receptor by PDZ domain-containing proteins. J Neurochem 2004;89:100–108. [PubMed: 15030393]

Jensen V, Kaiser KM, Borchardt T, Adelmann G, Rozov A, Burnashev N, et al. A juvenile form of postsynaptic hippocampal long-term potentiation in mice deficient for the AMPA receptor subunit GluR-A. J Physiol 2003;553:843–856. [PubMed: 14555717]

Ju W, Morishita W, Tsui J, Gaietta G, Deerinck TJ, Adams SR, et al. Activity-dependent regulation of dendritic synthesis and trafficking of AMPA receptors. Nat Neurosci 2004;7:244–253. [PubMed: 14770185]

Kalia LV, Gingrich JR, Salter MW. Src in synaptic transmission and plasticity. Oncogene 2004;23:8007–8016. [PubMed: 15489918]

Kameyama K, Lee HK, Bear MF, Huganir RL. Involvement of a postsynaptic protein kinase A substrate in the expression of homosynaptic long-term depression. Neuron 1998;21:1163–1175. [PubMed: 9856471]

Kauer JA, Malenka RC, Nicoll RA. A persistent postsynaptic modification mediates long-term potentiation in the hippocampus. Neuron 1988;1:911–917. [PubMed: 2908443]

Keller BU, Hollmann M, Heinemann S, Konnerth A. Calcium influx through subunits GluR1/GluR3 of kainate/AMPA receptor channels is regulated by cAMP dependent protein kinase. EMBO J 1992;11:891–896. [PubMed: 1372254]

Kennedy MB, Bennett MK, Erondu NE. Biochemical and immunochemical evidence that the “major postsynaptic density protein” is a subunit of a calmodulin-dependent protein kinase. Proc Natl Acad Sci U S A 1983;80:7357–7361. [PubMed: 6580651]

Kim CH, Chung HJ, Lee HK, Huganir RL. Interaction of the AMPA receptor subunit GluR2/3 with PDZ domains regulates hippocampal long-term depression. Proc Natl Acad Sci U S A 2001;98:11725–11730. [PubMed: 11573007]

Kleppisch T, Pfeifer A, Klatt P, Ruth P, Montkowski A, Fassler R, et al. Long-term potentiation in the hippocampal CA1 region of mice lacking cGMP-dependent kinases is normal and susceptible to inhibition of nitric oxide synthase. J Neurosci 1999;19:48–55. [PubMed: 9870937]

Kohr G, Seeburg PH. Subtype-specific regulation of recombinant NMDA receptor-channels by protein tyrosine kinases of the src family. J Physiol 1996;492(Pt 2):445–452. [PubMed: 9019541]

Kolleker A, Zhu JJ, Schupp BJ, Qin Y, Mack V, Borchardt T, et al. Glutamatergic plasticity by synaptic delivery of GluR-B(long)-containing AMPA receptors. Neuron 2003;40:1199–1212. [PubMed: 14687553]

Kolodziej SJ, Hudmon A, Waxham MN, Stoops JK. Three-dimensional reconstructions of calcium/calmodulin-dependent (CaM) kinase IIalpha and truncated CaM kinase IIalpha reveal a unique organization for its structural core and functional domains. J Biol Chem 2000;275:14354–14359. [PubMed: 10799516]

Krucker T, Siggins GR, McNamara RK, Lindsley KA, Dao A, Allison DW, et al. Targeted disruption of RC3 reveals a calmodulin-based mechanism for regulating metaplasticity in the hippocampus. J Neurosci 2002;22:5525–5535. [PubMed: 12097504]

Krupp JJ, Vissel B, Thomas CG, Heinemann SF, Westbrook GL. Calcineurin acts via the C-terminus of NR2A to modulate desensitization of NMDA receptors. Neuropharmacology 2002;42:593–602. [PubMed: 11985816]

Lai Y, Nairn AC, Greengard P. Autophosphorylation reversibly regulates the Ca^{2+}/calmodulin-dependence of Ca^{2+}/calmodulin-dependent protein kinase II. Proc Natl Acad Sci U S A 1986;83:4253–4257. [PubMed: 3012560]

Lan JY, Skeberdis VA, Jover T, Grooms SY, Lin Y, Araneda RC, et al. Protein kinase C modulates NMDA receptor trafficking and gating. Nat Neurosci 2001;4:382–390. [PubMed: 11276228]

Lau LF, Huganir RL. Differential tyrosine phosphorylation of *N*-methyl-d-aspartate receptor subunits. J Biol Chem 1995;270:20036–20041. [PubMed: 7544350]

Lavezzari G, McCallum J, Dewey CM, Roche KW. Subunit-specific regulation of NMDA receptor endocytosis. J Neurosci 2004;24:6383–6391. [PubMed: 15254094]

Lee, HK. AMPA receptor phosphorylation in synaptic plasticity: insights from knockin mice. In: Kittler, J.; Moss, SJ., editors. The Dynamic Synapse: Molecular Methods in Ionotropic Receptor Biology. Boca Raton, FL: CRC Press; 2006.

Lee HK, Kameyama K, Huganir RL, Bear MF. NMDA induces long-term synaptic depression and dephosphorylation of the GluR1 subunit of AMPA receptors in hippocampus. Neuron 1998;21:1151–1162. [PubMed: 9856470]

Lee HK, Barbarosie M, Kameyama K, Bear MF, Huganir RL. Regulation of distinct AMPA receptor phosphorylation sites during bidirectional synaptic plasticity. Nature 2000;405:955–959. [PubMed: 10879537]

Lee HK, Takamiya K, Kameyama K, Yu S, Rossetti L, He C, et al. Identification and characterization of a novel phosphorylation site on the GluR1 subunit of AMPA receptors. Soc Neurosci 2002:747.14.

Lee HK, Takamiya K, Han JS, Man H, Kim CH, Rumbaugh G, et al. Phosphorylation of the AMPA receptor GluR1 subunit is required for synaptic plasticity and retention of spatial memory. Cell 2003;112:631–643. [PubMed: 12628184]

Lee HK, Takamiya K, Yu S, Huganir RL. Dissecting out the role of specific AMPA receptor GluR1 phosphorylation sites in long-term potentiation and long-term depression. Soc Neurosci 2004:971.8.

Leonard AS, Hell JW. Cyclic AMP-dependent protein kinase and protein kinase C phosphorylate *N*-methyl-d-aspartate receptors at different sites. J Biol Chem 1997;272:12107–12115. [PubMed: 9115280]

Leonard AS, Davare MA, Horne MC, Garner CC, Hell JW. SAP97 is associated with the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor GluR1 subunit. J Biol Chem 1998;273:19518–19524. [PubMed: 9677374]

Leonard AS, Lim IA, Hemsworth DE, Horne MC, Hell JW. Calcium/calmodulin-dependent protein kinase II is associated with the *N*-methyl-d-aspartate receptor. Proc Natl Acad Sci U S A 1999;96:3239–3244. [PubMed: 10077668]

Letts VA. Stargazer-a mouse to seize! Epilepsy Curr 2005;5:161–165. [PubMed: 16175212]

Liao GY, Kreitzer MA, Sweetman BJ, Leonard JP. The postsynaptic density protein PSD95 differentially regulates insulin- and Src-mediated current modulation of mouse NMDA receptors expressed in Xenopus oocytes. J Neurochem 2000;75:282–287. [PubMed: 10854272]

Liao GY, Wagner DA, Hsu MH, Leonard JP. Evidence for direct protein kinase-C mediated modulation of *N*-methyl-d-aspartate receptor current. Mol Pharmacol 2001;59:960–964. [PubMed: 11306676]

Lickteig R, Shenolikar S, Denner L, Kelly PT. Regulation of Ca^{2+}/calmodulin-dependent protein kinase II by Ca^{2+}/calmodulin-independent autophosphorylation. J Biol Chem 1988;263:19232–19239. [PubMed: 2848818]

Ling DS, Benardo LS, Serrano PA, Blace N, Kelly MT, Crary JF, et al. Protein kinase Mzeta is necessary and sufficient for LTP maintenance. Nat Neurosci 2002;5:295–296. [PubMed: 11914719]

Lisman JE. A mechanism for memory storage insensitive to molecular turnover: a bistable autophosphorylating kinase. Proc Natl Acad Sci U S A 1985;82:3055–3057. [PubMed: 2986148]

Lisman J. A mechanism for the Hebb and the anti-Hebb processes underlying learning and memory. Proc Natl Acad Sci U S A 1989;86:9574–9578. [PubMed: 2556718]

Lisman J. The CaM kinase II hypothesis for the storage of synaptic memory. Trends Neurosci 1994;17:406–412. [PubMed: 7530878]

Lisman JE, Zhabotinsky AM. A model of synaptic memory: a CaMKII/PP1 switch that potentiates transmission by organizing an AMPA receptor anchoring assembly. Neuron 2001;31:191–201. [PubMed: 11502252]

Lisman J, Schulman H, Cline H. The molecular basis of CaMKII function in synaptic and behavioural memory. Nat Rev Neurosci 2002;3:175–190. [PubMed: 11994750]

Lissin DV, Gomperts SN, Carroll RC, Christine CW, Kalman D, Kitamura M, et al. Activity differentially regulates the surface expression of synaptic AMPA and NMDA glutamate receptors. Proc Natl Acad Sci U S A 1998;95:7097–7102. [PubMed: 9618545]

Liu L, Wong TP, Pozza MF, Lingenhoehl K, Wang Y, Sheng M, et al. Role of NMDA receptor subtypes in governing the direction of hippocampal synaptic plasticity. Science 2004;304:1021–1024. [PubMed: 15143284]

Lledo PM, Hjelmstad GO, Mukherji S, Soderling TR, Malenka RC, Nicoll RA. Calcium/calmodulin-dependent kinase II and long-term potentiation enhance synaptic transmission by the same mechanism. Proc Natl Acad Sci U S A 1995;92:11175–11179. [PubMed: 7479960]

Lou LL, Schulman H. Distinct autophosphorylation sites sequentially produce autonomy and inhibition of the multifunctional Ca^{2+}/calmodulin-dependent protein kinase. J Neurosci 1989;9:2020–2032. [PubMed: 2542484]

Lovinger DM, Wong KL, Murakami K, Routtenberg A. Protein kinase C inhibitors eliminate hippocampal long-term potentiation. Brain Res 1987;436:177–183. [PubMed: 2825923]

Lu W, Ziff EB. PICK1 interacts with ABP/GRIP to regulate AMPA receptor trafficking. Neuron 2005;47:407–421. [PubMed: 16055064]

Lu YM, Roder JC, Davidow J, Salter MW. Src activation in the induction of long-term potentiation in CA1 hippocampal neurons. Science 1998;279:1363–1367. [PubMed: 9478899]

Lu YF, Kandel ER, Hawkins RD. Nitric oxide signaling contributes to late-phase LTP and CREB phosphorylation in the hippocampus. J Neurosci 1999;19:10250–10261. [PubMed: 10575022]

Lu YM, Mansuy IM, Kandel ER, Roder J. Calcineurin-mediated LTD of GABAergic inhibition underlies the increased excitability of CA1 neurons associated with LTP. Neuron 2000;26:197–205. [PubMed: 10798404]

Luthi A, Wikstrom MA, Palmer MJ, Matthews P, Benke TA, Isaac JT, et al. Bi-directional modulation of AMPA receptor unitary conductance by synaptic activity. BMC Neurosci 2004;5:44. [PubMed: 15538948]

Mack V, Burnashev N, Kaiser KM, Rozov A, Jensen V, Hvalby O, et al. Conditional restoration of hippocampal synaptic potentiation in Glur-A-deficient mice. Science 2001;292:2501–2504. [PubMed: 11431570]

Madden DR. The structure and function of glutamate receptor ion channels. Nat Rev Neurosci 2002;3:91–101. [PubMed: 11836517]

Maffei A, Nelson SB, Turrigiano GG. Selective reconfiguration of layer 4 visual cortical circuitry by visual deprivation. Nat Neurosci 2004;7:1353–1359. [PubMed: 15543139]

Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron 2004;44:5–21. [PubMed: 15450156]

Malenka RC, Kauer JA, Perkel DJ, Mauk MD, Kelly PT, Nicoll RA, et al. An essential role for postsynaptic calmodulin and protein kinase activity in long-term potentiation. Nature 1989;340:554–557. [PubMed: 2549423]

Malinow R, Schulman H, Tsien RW. Inhibition of postsynaptic PKC or CaMKII blocks induction but not expression of LTP. Science 1989;245:862–866. [PubMed: 2549638]

Malleret G, Haditsch U, Genoux D, Jones MW, Bliss TV, Vanhoose AM, et al. Inducible and reversible enhancement of learning, memory, and long-term potentiation by genetic inhibition of calcineurin. Cell 2001;104:675–686. [PubMed: 11257222]

Mammen AL, Kameyama K, Roche KW, Huganir RL. Phosphorylation of the alpha-amino-3-hydroxy-5-methylisoxazole4-propionic acid receptor GluR1 subunit by calcium/calmodulin-dependent kinase II. J Biol Chem 1997;272:32528–32533. [PubMed: 9405465]

Martin LJ, Blackstone CD, Levey AI, Huganir RL, Price DL. AMPA glutamate receptor subunits are differentially distributed in rat brain. Neuroscience 1993;53:327–358. [PubMed: 8388083]

Massey PV, Johnson BE, Moult PR, Auberson YP, Brown MW, Molnar E, et al. Differential roles of NR2A and NR2B-containing NMDA receptors in cortical long-term potentiation and long-term depression. J Neurosci 2004;24:7821–7828. [PubMed: 15356193]

Matsubara M, Kusubata M, Ishiguro K, Uchida T, Titani K, Taniguchi H. Site-specific phosphorylation of synapsin I by mitogen-activated protein kinase and Cdk5 and its effects on physiological functions. J Biol Chem 1996;271:21108–21113. [PubMed: 8702879]

Matsuda S, Mikawa S, Hirai H. Phosphorylation of serine-880 in GluR2 by protein kinase C prevents its C terminus from binding with glutamate receptor-interacting protein. J Neurochem 1999;73:1765–1768. [PubMed: 10501226]

Matthies H, Reymann KG. Protein kinase A inhibitors prevent the maintenance of hippocampal long-term potentiation. NeuroReport 1993;4:712–714. [PubMed: 8347813]

Mauceri D, Cattabeni F, Di Luca M, Gardoni F. Calcium/calmodulin-dependent protein kinase II phosphorylation drives synapse-associated protein 97 into spines. J Biol Chem 2004;279:23813–23821. [PubMed: 15044483]

Mayer ML, Westbrook GL, Guthrie PB. Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurones. Nature 1984;309:261–263. [PubMed: 6325946]

Mayford M, Wang J, Kandel ER, O'Dell TJ. CaMKII regulates the frequency-response function of hippocampal synapses for the production of both LTD and LTP. Cell 1995;81:891–904. [PubMed: 7781066]

McDonald BJ, Chung HJ, Huganir RL. Identification of protein kinase C phosphorylation sites within the AMPA receptor GluR2 subunit. Neuropharmacology 2001;41:672–679. [PubMed: 11640921]

Miller KD. Synaptic economics: competition and cooperation in synaptic plasticity. Neuron 1996;17:371–374. [PubMed: 8816700]

Miller SG, Kennedy MB. Regulation of brain type II Ca^{2+}/calmodulin-dependent protein kinase by autophosphorylation: a Ca^{2+}-triggered molecular switch. Cell 1986;44:861–870. [PubMed: 3006921]

Miura M, Watanabe M, Offermanns S, Simon MI, Kano M. Group I metabotropic glutamate receptor signaling via Galpha q/Galpha 11 secures the induction of long-term potentiation in the hippocampal area CA1. J Neurosci 2002;22:8379–8390. [PubMed: 12351712]

Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg PH. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. Neuron 1994;12:529–540. [PubMed: 7512349]

Morishita W, Marie H, Malenka RC. Distinct triggering and expression mechanisms underlie LTD of AMPA and NMDA synaptic responses. Nat Neurosci 2005;8:1043–1050. [PubMed: 16025109]

Moss SJ, Blackstone CD, Huganir RL. Phosphorylation of recombinant non-NMDA glutamate receptors on serine and tyrosine residues. Neurochem Res 1993;18:105–110. [PubMed: 7681938]

Mu Y, Otsuka T, Horton AC, Scott DB, Ehlers MD. Activity-dependent mRNA splicing controls ER export and synaptic delivery of NMDA receptors. Neuron 2003;40:581–594. [PubMed: 14642281]

Mulkey RM, Malenka RC. Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. Neuron 1992;9:967–975. [PubMed: 1419003]

Mulkey RM, Herron CE, Malenka RC. An essential role for protein phosphatases in hippocampal long-term depression. Science 1993;261:1051–1055. [PubMed: 8394601]

Mulkey RM, Endo S, Shenolikar S, Malenka RC. Involvement of a calcineurin/inhibitor-1 phosphatase cascade in hippocampal long-term depression. Nature 1994;369:486–488. [PubMed: 7515479]

Naie K, Manahan-Vaughan D. Regulation by metabotropic glutamate receptor 5 of LTP in the dentate gyrus of freely moving rats: relevance for learning and memory formation. Cereb Cortex 2004;14:189–198. [PubMed: 14704216]

Nakagawa T, Cheng Y, Ramm E, Sheng M, Walz T. Structure and different conformational states of native AMPA receptor complexes. Nature 2005;433:545–549. [PubMed: 15690046]

Nakanishi N, Shneider NA, Axel R. A family of glutamate receptor genes: evidence for the formation of heteromultimeric receptors with distinct channel properties. Neuron 1990;5:569–581. [PubMed: 1699567]

Nakazawa T, Komai S, Tezuka T, Hisatsune C, Umemori H, Semba K, et al. Characterization of Fyn-mediated tyrosine phosphorylation sites on GluR epsilon 2 (NR2B) subunit of the *N*-methyl-d-aspartate receptor. J Biol Chem 2001;276:693–699. [PubMed: 11024032]

Neyton J, Paoletti P. Relating NMDA receptor function to receptor subunit composition: limitations of the pharmacological approach. J Neurosci 2006;26:1331–1333. [PubMed: 16452656]

Nguyen PV, Woo NH. Regulation of hippocampal synaptic plasticity by cyclic AMP-dependent protein kinases. Prog Neurobiol 2003;71:401–437. [PubMed: 15013227]

Nicoll RA, Tomita S, Bredt DS. Auxiliary subunits assist AMPA-type glutamate receptors. Science 2006;311:1253–1256. [PubMed: 16513974]

Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A. Magnesium gates glutamate-activated channels in mouse central neurones. Nature 1984;307:462–465. [PubMed: 6320006]

O'Brien RJ, Kamboj S, Ehlers MD, Rosen KR, Fischbach GD, Huganir RL. Activity-dependent modulation of synaptic AMPA receptor accumulation. Neuron 1998;21:1067–1078. [PubMed: 9856462]

O'Dell TJ, Kandel ER, Grant SG. Long-term potentiation in the hippocampus is blocked by tyrosine kinase inhibitors. Nature 1991;353:558–560. [PubMed: 1656271]

Oh MC, Derkach VA. Dominant role of the GluR2 subunit in regulation of AMPA receptors by CaMKII. Nat Neurosci 2005;8:853–854. [PubMed: 15924137]

Oh MC, Derkach VA, Guire ES, Soderling TR. Extrasynaptic membrane trafficking regulated by GluR1 serine 845 phosphorylation primes AMPA receptors for long-term potentiation. J Biol Chem 2006;281:752–758. [PubMed: 16272153]

Omkumar RV, Kiely MJ, Rosenstein AJ, Min KT, Kennedy MB. Identification of a phosphorylation site for calcium/calmodulindependent protein kinase II in the NR2B subunit of the *N*-methyl-d-aspartate receptor. J Biol Chem 1996;271:31670–31678. [PubMed: 8940188]

Osten P, Khatri L, Perez JL, Kohr G, Giese G, Daly C, et al. Mutagenesis reveals a role for ABP/GRIP binding to GluR2 in synaptic surface accumulation of the AMPA receptor. Neuron 2000;27:313–325. [PubMed: 10985351]

Otmakhov N, Griffith LC, Lisman JE. Postsynaptic inhibitors of calcium/calmodulin-dependent protein kinase type II block induction but not maintenance of pairing-induced long-term potentiation. J Neurosci 1997;17:5357–5365. [PubMed: 9204920]

Otmakhov N, Tao-Cheng JH, Carpenter S, Asrican B, Dosemeci A, Reese TS, et al. Persistent accumulation of calcium/calmodulin-dependent protein kinase II in dendritic spines after induction of NMDA receptor-dependent chemical long-term potentiation. J Neurosci 2004;24:9324–9331. [PubMed: 15496668]

Otmakhova NA, Otmakhov N, Mortenson LH, Lisman JE. Inhibition of the cAMP pathway decreases early long-term potentiation at CA1 hippocampal synapses. J Neurosci 2000;20:4446–4451. [PubMed: 10844013]

Ouyang Y, Kantor D, Harris KM, Schuman EM, Kennedy MB. Visualization of the distribution of autophosphorylated calcium/calmodulin-dependent protein kinase II after tetanic stimulation in the CA1 area of the hippocampus. J Neurosci 1997;17:5416–5427. [PubMed: 9204925]

Ouyang Y, Rosenstein A, Kreiman G, Schuman EM, Kennedy MB. Tetanic stimulation leads to increased accumulation of $Ca(^{2+})$/calmodulin-dependent protein kinase II via dendritic protein synthesis in hippocampal neurons. J Neurosci 1999;19:7823–7833. [PubMed: 10479685]

Pak JH, Huang FL, Li J, Balschun D, Reymann KG, Chiang C, et al. Involvement of neurogranin in the modulation of calcium/calmodulin-dependent protein kinase II, synaptic plasticity, and spatial learning: a study with knockout mice. Proc Natl Acad Sci U S A 2000;97:11232–11237. [PubMed: 11016969]

Palmer MJ, Isaac JT, Collingridge GL. Multiple, developmentally regulated expression mechanisms of long-term potentiation at CA1 synapses. J Neurosci 2004;24:4903–4911. [PubMed: 15163681]

Patton BL, Miller SG, Kennedy MB. Activation of type II calcium/calmodulin-dependent protein kinase by Ca^{2+}/calmodulin is inhibited by autophosphorylation of threonine within the calmodulin-binding domain. J Biol Chem 1990;265:11204–11212. [PubMed: 2162838]

Pelkey KA, Askalan R, Paul S, Kalia LV, Nguyen TH, Pitcher GM, et al. Tyrosine phosphatase STEP is a tonic brake on induction of long-term potentiation. Neuron 2002;34:127–138. [PubMed: 11931747]

Peng J, Kim MJ, Cheng D, Duong DM, Gygi SP, Sheng M. Semiquantitative proteomic analysis of rat forebrain postsynaptic density fractions by mass spectrometry. J Biol Chem 2004;279:21003–21011. [PubMed: 15020595]

Perez JL, Khatri L, Chang C, Srivastava S, Osten P, Ziff EB. PICK1 targets activated protein kinase Calpha to AMPA receptor clusters in spines of hippocampal neurons and reduces surface levels of the AMPA-type glutamate receptor subunit 2. J Neurosci 2001;21:5417–5428. [PubMed: 11466413]

Perez-Otano I, Ehlers MD. Homeostatic plasticity and NMDA receptor trafficking. Trends Neurosci 2005;28:229–238. [PubMed: 15866197]

Petralia RS, Wenthold RJ. Light and electron immunocytochemical localization of AMPA-selective glutamate receptors in the rat brain. J Comp Neurol 1992;318:329–354. [PubMed: 1374769]

Pettit DL, Perlman S, Malinow R. Potentiated transmission and prevention of further LTP by increased CaMKII activity in postsynaptic hippocampal slice neurons. Science 1994;266:1881–1885. [PubMed: 7997883]

Philpot BD, Sekhar AK, Shouval HZ, Bear MF. Visual experience and deprivation bidirectionally modify the composition and function of NMDA receptors in visual cortex. Neuron 2001;29:157–169. [PubMed: 11182088]

Philpot BD, Espinosa JS, Bear MF. Evidence for altered NMDA receptor function as a basis for metaplasticity in visual cortex. J Neurosci 2003;23:5583–5588. [PubMed: 12843259]

Pisano MR, Hegazy MG, Reimann EM, Dokas LA. Phosphorylation of protein B-50 (GAP-43) from adult rat brain cortex by casein kinase II. Biochem Biophys Res Commun 1988;155:1207–1212. [PubMed: 3178803]

Poncer JC, Esteban JA, Malinow R. Multiple mechanisms for the potentiation of AMPA receptor-mediated transmission by alpha-Ca^{2+}/calmodulin-dependent protein kinase II. J Neurosci 2002;22:4406–4411. [PubMed: 12040047]

Prichard L, Deloulme JC, Storm DR. Interactions between neurogranin and calmodulin in vivo. J Biol Chem 1999;274:7689–7694. [PubMed: 10075657]

Priel A, Kolleker A, Ayalon G, Gillor M, Osten P, Stern-Bach Y. Stargazin reduces desensitization and slows deactivation of the AMPA-type glutamate receptors. J Neurosci 2005;25:2682–2686. [PubMed: 15758178]

Prybylowski K, Chang K, Sans N, Kan L, Vicini S, Wenthold RJ. The synaptic localization of NR2B-containing NMDA receptors is controlled by interactions with PDZ proteins and AP-2. Neuron 2005;47:845–857. [PubMed: 16157279]

Qi M, Zhuo M, Skalhegg BS, Brandon EP, Kandel ER, McKnight GS, et al. Impaired hippocampal plasticity in mice lacking the Cbeta1 catalytic subunit of cAMP-dependent protein kinase. Proc Natl Acad Sci U S A 1996;93:1571–1576. [PubMed: 8643673]

Quinlan EM, Olstein DH, Bear MF. Bidirectional, experience-dependent regulation of *N*-methyl-d-aspartate receptor subunit composition in the rat visual cortex during postnatal development. Proc Natl Acad Sci U S A 1999;96:12876–12880. [PubMed: 10536016]

Quinlan EM, Philpot BD, Huganir RL, Bear MF. Rapid, experience-dependent expression of synaptic NMDA receptors in visual cortex in vivo. Nat Neurosci 1999;2:352–357. [PubMed: 10204542]

Quinlan EM, Lebel D, Brosh I, Barkai E. A molecular mechanism for stabilization of learning-induced synaptic modifications. Neuron 2004;41:185–192. [PubMed: 14741100]

Ramakers GM, Pasinelli P, Hens JJ, Gispen WH, De Graan PN. Protein kinase C in synaptic plasticity: changes in the in situ phosphorylation state of identified pre- and postsynaptic substrates. Prog Neuropsychopharmacol Biol Psychiatry 1997;21:455–486. [PubMed: 9153068]

Ramakers GM, Gerendasy DD, de Graan PN. Substrate phosphorylation in the protein kinase Cgamma knockout mouse. J Biol Chem 1999;274:1873–1874. [PubMed: 9890937]

Raman IM, Tong G, Jahr CE. Beta-adrenergic regulation of synaptic NMDA receptors by cAMP-dependent protein kinase. Neuron 1996;16:415–421. [PubMed: 8789956]

Raymond CR, Thompson VL, Tate WP, Abraham WC. Metabotropic glutamate receptors trigger homosynaptic protein synthesis to prolong long-term potentiation. J Neurosci 2000;20:969–976. [PubMed: 10648701]

Represa A, Deloulme JC, Sensenbrenner M, Ben-Ari Y, Baudier J. Neurogranin: immunocytochemical localization of a brain-specific protein kinase C substrate. J Neurosci 1990;10:3782–3792. [PubMed: 2269883]

Reymann KG, Brodemann R, Kase H, Matthies H. Inhibitors of calmodulin and protein kinase C block different phases of hippocampal long-term potentiation. Brain Res 1988;461:388–392. [PubMed: 3179724]

Reymann KG, Frey U, Jork R, Matthies H. Polymyxin B, an inhibitor of protein kinase C, prevents the maintenance of synaptic long-term potentiation in hippocampal CA1 neurons. Brain Res 1988;440:305–314. [PubMed: 2833996]

Rioult-Pedotti MS, Friedman D, Donoghue JP. Learning-induced LTP in neocortex. Science 2000;290:533–536. [PubMed: 11039938]

Roberson ED, Sweatt JD. Transient activation of cyclic AMP-dependent protein kinase during hippocampal long-term potentiation. J Biol Chem 1996;271:30436–30441. [PubMed: 8940008]

Roberson, ED.; English, JD.; Sweatt, JD. Second messengers in LTP and LTD. In: Fazeli, MS.; Collingridge, GL., editors. Cortical Plasiticity. Oxford: BIOS Scientific Publishers; 1996. p. 35-60.

Roche KW, O'Brien RJ, Mammen AL, Bernhardt J, Huganir RL. Characterization of multiple phosphorylation sites on the AMPA receptor GluR1 subunit. Neuron 1996;16:1179–1188. [PubMed: 8663994]

Roche KW, Standley S, McCallum J, Dune Ly C, Ehlers MD, Wenthold RJ. Molecular determinants of NMDA receptor internalization. Nat Neurosci 2001;4:794–802. [PubMed: 11477425]

Rogan MT, Staubli UV, LeDoux JE. Fear conditioning induces associative long-term potentiation in the amygdala. Nature 1997;390:604–607. [PubMed: 9403688]

Rosenblum K, Dudai Y, Richter-Levin G. Long-term potentiation increases tyrosine phosphorylation of the *N*-methyl-d-aspartate receptor subunit 2B in rat dentate gyrus in vivo. Proc Natl Acad Sci U S A 1996;93:10457–10460. [PubMed: 8816822]

Rosenmund C, Carr DW, Bergeson SE, Nilaver G, Scott JD, Westbrook GL. Anchoring of protein kinase A is required for modulation of AMPA/kainate receptors on hippocampal neurons. Nature 1994;368:853–856. [PubMed: 8159245]

Rostas JA, Brent VA, Voss K, Errington ML, Bliss TV, Gurd JW. Enhanced tyrosine phosphorylation of the 2B subunit of the *N*-methyl-d-aspartate receptor in long-term potentiation. Proc Natl Acad Sci U S A 1996;93:10452–10456. [PubMed: 8816821]

Rouach N, Byrd K, Petralia RS, Elias GM, Adesnik H, Tomita S, et al. TARP gamma-8 controls hippocampal AMPA receptor number, distribution and synaptic plasticity. Nat Neurosci 2005;8:1525–1533. [PubMed: 16222232]

Rutherford LC, Nelson SB, Turrigiano GG. BDNF has opposite effects on the quantal amplitude of pyramidal neuron and interneuron excitatory synapses. Neuron 1998;21:521–530. [PubMed: 9768839]

Sacktor TC, Osten P, Valsamis H, Jiang X, Naik MU, Sublette E. Persistent activation of the zeta isoform of protein kinase C in the maintenance of long-term potentiation. Proc Natl Acad Sci U S A 1993;90:8342–8346. [PubMed: 8378304]

Salter MW, Kalia LV. Src kinases: a hub for NMDA receptor regulation. Nat Rev Neurosci 2004;5:317–328. [PubMed: 15034556]

Sanchez-Perez AM, Felipo V. Serines 890 and 896 of the NMDA receptor subunit NR1 are differentially phosphorylated by protein kinase C isoforms. Neurochem Int 2005;47:84–91. [PubMed: 15936117]

Sanes JR, Lichtman JW. Can molecules explain long-term potentiation? Nat Neurosci 1999;2:597–604. [PubMed: 10404178]

Sans N, Petralia RS, Wang YX, Blahos J II, Hell JW, Wenthold RJ. A developmental change in NMDA receptor-associated proteins at hippocampal synapses. J Neurosci 2000;20:1260–1271. [PubMed: 10648730]

Sans N, Racca C, Petralia RS, Wang YX, McCallum J, Wenthold RJ. Synapse-associated protein 97 selectively associates with a subset of AMPA receptors early in their biosynthetic pathway. J Neurosci 2001;21:7506–7516. [PubMed: 11567040]

Sawtell NB, Frenkel MY, Philpot BD, Nakazawa K, Tonegawa S, Bear MF. NMDA receptor-dependent ocular dominance plasticity in adult visual cortex. Neuron 2003;38:977–985. [PubMed: 12818182]

Schnell E, Sizemore M, Karimzadegan S, Chen L, Bredt DS, Nicoll RA. Direct interactions between PSD95 and stargazin control synaptic AMPA receptor number. Proc Natl Acad Sci U S A 2002;99:13902–13907. [PubMed: 12359873]

Schworer CM, Colbran RJ, Soderling TR. Reversible generation of a Ca^{2+}-independent form of Ca^{2+} (calmodulin)-dependent protein kinase II by an autophosphorylation mechanism. J Biol Chem 1986;261:8581–8584. [PubMed: 3722161]

Schworer CM, Colbran RJ, Keefer JR, Soderling TR. Ca^{2+}/calmodulin-dependent protein kinase II. Identification of a regulatory autophosphorylation site adjacent to the inhibitory and calmodulin-binding domains. J Biol Chem 1988;263:13486–13489. [PubMed: 3417668]

Scott DB, Blanpied TA, Swanson GT, Zhang C, Ehlers MD. An NMDA receptor ER retention signal regulated by phosphorylation and alternative splicing. J Neurosci 2001;21:3063–3072. [PubMed: 11312291]

Scott DB, Blanpied TA, Ehlers MD. Coordinated PKA and PKC phosphorylation suppresses RXR-mediated ER retention and regulates the surface delivery of NMDA receptors. Neuropharmacology 2003;45:755–767. [PubMed: 14529714]

Seeburg PH, Hartner J. Regulation of ion channel/neurotransmitter receptor function by RNA editing. Curr Opin Neurobiol 2003;13:279–283. [PubMed: 12850211]

Seidenman KJ, Steinberg JP, Huganir R, Malinow R. Glutamate receptor subunit 2 Serine 880 phosphorylation modulates synaptic transmission and mediates plasticity in CA1 pyramidal cells. J Neurosci 2003;23:9220–9228. [PubMed: 14534256]

Selcher JC, Nekrasova T, Paylor R, Landreth GE, Sweatt JD. Mice lacking the ERK1 isoform of MAP kinase are unimpaired in emotional learning. Learn Mem 2001;8:11–19. [PubMed: 11160759]

Selcher JC, Weeber EJ, Christian J, Nekrasova T, Landreth GE, Sweatt JD. A role for ERK MAP kinase in physiologic temporal integration in hippocampal area CA1. Learn Mem 2003;10:26–39. [PubMed: 12551961]

Selig DK, Segal MR, Liao D, Malenka RC, Malinow R, Nicoll RA, et al. Examination of the role of cGMP in long-term potentiation in the CA1 region of the hippocampus. Learn Mem 1996;3:42–48. [PubMed: 10456075]

Serrano P, Yao Y, Sacktor TC. Persistent phosphorylation by protein kinase Mzeta maintains late-phase long-term potentiation. J Neurosci 2005;25:1979–1984. [PubMed: 15728837]

Shen K, Meyer T. Dynamic control of CaMKII translocation and localization in hippocampal neurons by NMDA receptor stimulation. Science 1999;284:162–166. [PubMed: 10102820]

Shen K, Teruel MN, Subramanian K, Meyer T. CaMKIIbeta functions as an F-actin targeting module that localizes CaMKIIalpha/beta heterooligomers to dendritic spines. Neuron 1998;21:593–606. [PubMed: 9768845]

Shen K, Teruel MN, Connor JH, Shenolikar S, Meyer T. Molecular memory by reversible translocation of calcium/calmodulin-dependent protein kinase II. Nat Neurosci 2000;3:881–886. [PubMed: 10966618]

Sigel E, Baur R, Malherbe P. Protein kinase C transiently activated heteromeric *N*-methyl-d-aspartate receptor channels independent of the phosphorylatable C-terminal splice domain and of consensus phosphorylation sites. J Biol Chem 1994;269:8204–8208. [PubMed: 7510681]

Silva AJ, Stevens CF, Tonegawa S, Wang Y. Deficient hippocampal long-term potentiation in alpha-calcium-calmodulin kinase II mutant mice. Science 1992;257:201–206. [PubMed: 1378648]

Skeberdis VA, Chevaleyre V, Lau CG, Goldberg JH, Pettit DL, Suadicani SO, et al. Protein kinase A regulates calcium permeability of NMDA receptors. Nat Neurosci 2006;9:501–510. [PubMed: 16531999]

Smith KE, Gibson ES, Dell'Acqua ML. cAMP-dependent protein kinase postsynaptic localization regulated by NMDA receptor activation through translocation of an A-kinase anchoring protein scaffold protein. J Neurosci 2006;26:2391–2402. [PubMed: 16510716]

Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, et al. Regulation of NMDA receptor trafficking by amyloid-beta. Nat Neurosci 2005;8:1051–1058. [PubMed: 16025111]

Soderling TR. CaM-kinases: modulators of synaptic plasticity. Curr Opin Neurobiol 2000;10:375–380. [PubMed: 10851169]

Song I, Huganir RL. Regulation of AMPA receptors during synaptic plasticity. Trends Neurosci 2002;25:578–588. [PubMed: 12392933]

Srivastava S, Osten P, Vilim FS, Khatri L, Inman G, States B, et al. Novel anchorage of GluR2/3 to the postsynaptic density by the AMPA receptor-binding protein ABP. Neuron 1998;21:581–591. [PubMed: 9768844]

Stent GS. A physiological mechanism for Hebb's postulate of learning. Proc Natl Acad Sci U S A 1973;70:997–1001. [PubMed: 4352227]

Strack S, Colbran RJ. Autophosphorylation-dependent targeting of calcium/calmodulin-dependent protein kinase II by the NR2B subunit of the N-methyl- D-aspartate receptor. J Biol Chem 1998;273:20689–20692. [PubMed: 9694809]

Strack S, Barban MA, Wadzinski BE, Colbran RJ. Differential inactivation of postsynaptic density-associated and soluble Ca^{2+}/calmodulin-dependent protein kinase II by protein phosphatases 1 and 2A. J Neurochem 1997;68:2119–2128. [PubMed: 9109540]

Strack S, Choi S, Lovinger DM, Colbran RJ. Translocation of autophosphorylated calcium/calmodulin-dependent protein kinase II to the postsynaptic density. J Biol Chem 1997;272:13467–13470. [PubMed: 9153188]

Strack S, McNeill RB, Colbran RJ. Mechanism and regulation of calcium/calmodulin-dependent protein kinase II targeting to the NR2B subunit of the *N*-methyl-d-aspartate receptor. J Biol Chem 2000;275:23798–23806. [PubMed: 10764765]

Stumpo DJ, Graff JM, Albert KA, Greengard P, Blackshear PJ. Molecular cloning, characterization, and expression of a cDNA encoding the “80- to 87-kDa” myristoylated alanine-rich C kinase substrate: A major cellular substrate for protein kinase C. Proc Natl Acad Sci U S A 1989;86:4012–4016. [PubMed: 2726763]

Suen PC, Wu K, Xu JL, Lin SY, Levine ES, Black IB. NMDA receptor subunits in the postsynaptic density of rat brain: expression and phosphorylation by endogenous protein kinases. Brain Res Mol Brain Res 1998;59:215–228. [PubMed: 9729394]

Sweatt JD. The neuronal MAP kinase cascade: a biochemical signal integration system subserving synaptic plasticity and memory. J Neurochem 2001;76:1–10. [PubMed: 11145972]

Tanaka H, Grooms SY, Bennett MV, Zukin RS. The AMPAR subunit GluR2: still front and center-stage. Brain Res 2000;886:190–207. [PubMed: 11119696]

Tavalin SJ, Colledge M, Hell JW, Langeberg LK, Huganir RL, Scott JD. Regulation of GluR1 by the A-kinase anchoring protein 79 (AKAP79) signaling complex shares properties with long-term depression. J Neurosci 2002;22:3044–3051. [PubMed: 11943807]

Terashima A, Cotton L, Dev KK, Meyer G, Zaman S, Duprat F, et al. Regulation of synaptic strength and AMPA receptor subunit composition by PICK1. J Neurosci 2004;24:5381–5390. [PubMed: 15190111]

Thiagarajan TC, Piedras-Renteria ES, Tsien RW. alpha- and betaCaMKII. Inverse regulation by neuronal activity and opposing effects on synaptic strength. Neuron 2002;36:1103–1114. [PubMed: 12495625]

Thiagarajan TC, Lindskog M, Tsien RW. Adaptation to synaptic inactivity in hippocampal neurons. Neuron 2005;47:725–737. [PubMed: 16129401]

Thiel G, Czernik AJ, Gorelick F, Nairn AC, Greengard P. Ca^{2+}/calmodulin-dependent protein kinase II: identification of threonine-286 as the autophosphorylation site in the alpha subunit associated with the generation of Ca^{2+}-independent activity. Proc Natl Acad Sci U S A 1988;85:6337–6341. [PubMed: 2842767]

Thiels E, Norman ED, Barrionuevo G, Klann E. Transient and persistent increases in protein phosphatase activity during long-term depression in the adult hippocampus in vivo. Neuroscience 1998;86:1023–1029. [PubMed: 9697109]

Thiels E, Kanterewicz BI, Knapp LT, Barrionuevo G, Klann E. Protein phosphatase-mediated regulation of protein kinase C during long-term depression in the adult hippocampus in vivo. J Neurosci 2000;20:7199–7207. [PubMed: 11007876]

Thiels E, Lee H, Huganir RL. AMPA receptor phosphorylation during long-term depression in the adult hippocampus in vivo. Society for Neuroscience Abstract 2002:648.1.

Thomas GM, Huganir RL. MAPK cascade signalling and synaptic plasticity. Nat Rev Neurosci 2004;5:173–183. [PubMed: 14976517]

Tingley WG, Ehlers MD, Kameyama K, Doherty C, Ptak JB, Riley CT, et al. Characterization of protein kinase A and protein kinase C phosphorylation of the *N*-methyl-d-aspartate receptor NR1 subunit using phosphorylation site-specific antibodies. J Biol Chem 1997;272:5157–5166. [PubMed: 9030583]

Tomita S, Chen L, Kawasaki Y, Petralia RS, Wenthold RJ, Nicoll RA, et al. Functional studies and distribution define a family of transmembrane AMPA receptor regulatory proteins. J Cell Biol 2003;161:805–816. [PubMed: 12771129]

Tomita S, Stein V, Stocker TJ, Nicoll RA, Bredt DS. Bidirectional synaptic plasticity regulated by phosphorylation of stargazin-like TARPs. Neuron 2005;45:269–277. [PubMed: 15664178]

Turrigiano GG, Nelson SB. Hebb and homeostasis in neuronal plasticity. Curr Opin Neurobiol 2000;10:358–364. [PubMed: 10851171]

Turrigiano GG, Nelson SB. Homeostatic plasticity in the developing nervous system. Nat Rev Neurosci 2004;5:97–107. [PubMed: 14735113]

Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB. Activity-dependent scaling of quantal amplitude in neocortical neurons. Nature 1998;391:892–896. [PubMed: 9495341]

Valtschanoff JG, Burette A, Davare MA, Leonard AS, Hell JW, Weinberg RJ. SAP97 concentrates at the postsynaptic density in cerebral cortex. Eur J Neurosci 2000;12:3605–3614. [PubMed: 11029631]

van Dam EJ, Ruiter B, Kamal A, Ramakers GM, Gispen WH, de Graan PN. *N*-methyl-d-aspartate-induced long-term depression is associated with a decrease in postsynaptic protein kinase C substrate phosphorylation in rat hippocampal slices. Neurosci Lett 2002;320:129–132. [PubMed: 11852179]

Verdoorn TA, Burnashev N, Monyer H, Seeburg PH, Sakmann B. Structural determinants of ion flow through recombinant glutamate receptor channels. Science 1991;252:1715–1718. [PubMed: 1710829]

Vissel B, Krupp JJ, Heinemann SF, Westbrook GL. A use-dependent tyrosine dephosphorylation of NMDA receptors is independent of ion flux. Nat Neurosci 2001;4:587–596. [PubMed: 11369939]

Walikonis RS, Jensen ON, Mann M, Provance DW Jr, Mercer JA, Kennedy MB. Identification of proteins in the postsynaptic density fraction by mass spectrometry. J Neurosci 2000;20:4069–4080. [PubMed: 10818142]

Wang YT, Salter MW. Regulation of NMDA receptors by tyrosine kinases and phosphatases. Nature 1994;369:233–235. [PubMed: 7514272]

Wang YT, Yu XM, Salter MW. Ca($^{2+}$)-independent reduction of *N*-methyl-d-aspartate channel activity by protein tyrosine phosphatase. Proc Natl Acad Sci U S A 1996;93:1721–1725. [PubMed: 8643696]

Washburn MS, Numberger M, Zhang S, Dingledine R. Differential dependence on GluR2 expression of three characteristic features of AMPA receptors. J Neurosci 1997;17:9393–9406. [PubMed: 9390995]

Watson JB, Sutcliffe JG, Fisher RS. Localization of the protein kinase C phosphorylation/calmodulin-binding substrate RC3 in dendritic spines of neostriatal neurons. Proc Natl Acad Sci U S A 1992;89:8581–8585. [PubMed: 1528865]

Watson JB, Szijan I, Coulter PM II. Localization of RC3 (neurogranin) in rat brain subcellular fractions. Brain Res Mol Brain Res 1994;27:323–328. [PubMed: 7898318]

Watt AJ, van Rossum MC, MacLeod KM, Nelson SB, Turrigiano GG. Activity coregulates quantal AMPA and NMDA currents at neocortical synapses. Neuron 2000;26:659–670. [PubMed: 10896161]

Watt AJ, Sjostrom PJ, Hausser M, Nelson SB, Turrigiano GG. A proportional but slower NMDA potentiation follows AMPA potentiation in LTP. Nat Neurosci 2004;7:518–524. [PubMed: 15048122]

Weitlauf C, Honse Y, Auberson YP, Mishina M, Lovinger DM, Winder DG. Activation of NR2A-containing NMDA receptors is not obligatory for NMDA receptor-dependent long-term potentiation. J Neurosci 2005;25:8386–8390. [PubMed: 16162920]

Wenthold RJ, Yokotani N, Doi K, Wada K. Immunochemical characterization of the non-NMDA glutamate receptor using subunit-specific antibodies. Evidence for a hetero-oligomeric structure in rat brain. J Biol Chem 1992;267:501–507. [PubMed: 1309749]

Wenthold RJ, Petralia RS, Blahos J II, Niedzielski AS. Evidence for multiple AMPA receptor complexes in hippocampal CA1/CA2 neurons. J Neurosci 1996;16:1982–1989. [PubMed: 8604042]

Wikstrom MA, Matthews P, Roberts D, Collingridge GL, Bortolotto ZA. Parallel kinase cascades are involved in the induction of LTP at hippocampal CA1 synapses. Neuropharmacology 2003;45:828–836. [PubMed: 14529720]

Williams K, Russell SL, Shen YM, Molinoff PB. Developmental switch in the expression of NMDA receptors occurs in vivo and in vitro. Neuron 1993;10:267–278. [PubMed: 8439412]

Winder DG, Sweatt JD. Roles of serine/threonine phosphatases in hippocampal synaptic plasticity. Nat Rev Neurosci 2001;2:461–474. [PubMed: 11433371]

Winder DG, Mansuy IM, Osman M, Moallem TM, Kandel ER. Genetic and pharmacological evidence for a novel, intermediate phase of long-term potentiation suppressed by calcineurin. Cell 1998;92:25–37. [PubMed: 9489697]

Winder DG, Martin KC, Muzzio IA, Rohrer D, Chruscinski A, Kobilka B, et al. ERK plays a regulatory role in induction of LTP by theta frequency stimulation and its modulation by beta-adrenergic receptors. Neuron 1999;24:715–726. [PubMed: 10595521]

Wu WC, Walaas SI, Nairn AC, Greengard P. Calcium/phospholipid regulates phosphorylation of a Mr "87k" substrate protein in brain synaptosomes. Proc Natl Acad Sci U S A 1982;79:5249–5253. [PubMed: 6957862]

Wu J, Huang KP, Huang FL. Participation of NMDA-mediated phosphorylation and oxidation of neurogranin in the regulation of Ca^{2+}- and Ca^{2+}/calmodulin-dependent neuronal signaling in the hippocampus. J Neurochem 2003;86:1524–1533. [PubMed: 12950461]

Wu K, Len GW, McAuliffe G, Ma C, Tai JP, Xu F, et al. Brain-derived neurotrophic factor acutely enhances tyrosine phosphorylation of the AMPA receptor subunit GluR1 via NMDA receptor-dependent mechanisms. Brain Res Mol Brain Res 2004;130:178–186. [PubMed: 15519688]

Wyszynski M, Valtschanoff JG, Naisbitt S, Dunah AW, Kim E, Standaert DG, et al. Association of AMPA receptors with a subset of glutamate receptor-interacting protein in vivo. J Neurosci 1999;19:6528–6537. [PubMed: 10414981]

Xiao MY, Karpefors M, Gustafsson B, Wigstrom H. On the linkage between AMPA and NMDA receptor-mediated EPSPs in homosynaptic long-term depression in the hippocampal CA1 region of young rats. J Neurosci 1995;15:4496–4506. [PubMed: 7540677]

Xiong ZG, Pelkey KA, Lu WY, Lu YM, Roder JC, MacDonald JF, et al. Src potentiation of NMDA receptors in hippocampal and spinal neurons is not mediated by reducing zinc inhibition. J Neurosci 1999;19:RC37. [PubMed: 10531471]

Yang M, Leonard JP. Identification of mouse NMDA receptor subunit NR2A C-terminal tyrosine sites phosphorylated by coexpression with v-Src. J Neurochem 2001;77:580–588. [PubMed: 11299320]

Yang SN, Tang YG, Zucker RS. Selective induction of LTP and LTD by postsynaptic [Ca^{2+}]i elevation. J Neurophysiol 1999;81:781–787. [PubMed: 10036277]

Yasuda H, Barth AL, Stellwagen D, Malenka RC. A developmental switch in the signaling cascades for LTP induction. Nat Neurosci 2003;6:15–16. [PubMed: 12469130]

Yu XM, Askalan R, Keil GJ II, Salter MW. NMDA channel regulation by channel-associated protein tyrosine kinase Src. Science 1997;275:674–678. [PubMed: 9005855]

Zamanillo D, Sprengel R, Hvalby O, Jensen V, Burnashev N, Rozov A, et al. Importance of AMPA receptors for hippocampal synaptic plasticity but not for spatial learning. Science 1999;284:1805–1811. [PubMed: 10364547]

Zhang L, Kirschstein T, Sommersberg B, Merkens M, Manahan-Vaughan D, Elgersma Y, et al. Hippocampal synaptic metaplasticity requires inhibitory autophosphorylation of Ca^{2+}/calmodulin-dependent kinase II. J Neurosci 2005;25:7697–7707. [PubMed: 16107656]

Zheng F, Gingrich MB, Traynelis SF, Conn PJ. Tyrosine kinase potentiates NMDA receptor currents by reducing tonic zinc inhibition. Nat Neurosci 1998;1:185–191. [PubMed: 10195142]

Zheng X, Zhang L, Wang AP, Bennett MV, Zukin RS. Protein kinase C potentiation of *N*-methyl-d-aspartate receptor activity is not mediated by phosphorylation of *N*-methyl-d-aspartate receptor subunits. Proc Natl Acad Sci U S A 1999;96:15262–15267. [PubMed: 10611373]

Zhu JJ, Esteban JA, Hayashi Y, Malinow R. Postnatal synaptic potentiation: delivery of GluR4-containing AMPA receptors by spontaneous activity. Nat Neurosci 2000;3:1098–1106. [PubMed: 11036266]

Zhuo M, Hu Y, Schultz C, Kandel ER, Hawkins RD. Role of guanylyl cyclase and cGMP-dependent protein kinase in long-term potentiation. Nature 1994;368:635–639. [PubMed: 7908417]

Zhuo M, Zhang W, Son H, Mansuy I, Sobel RA, Seidman J, et al. A selective role of calcineurin aalpha in synaptic depotentiation in hippocampus. Proc Natl Acad Sci U S A 1999;96:4650–4655. [PubMed: 10200317]

Zukin RS, Bennett MV. Alternatively spliced isoforms of the NMDARI receptor subunit. Trends Neurosci 1995;18:306–313. [PubMed: 7571011]

Abbreviations

AKAP79/150
A-kinase anchoring protein 79/150

AMPA
α-amino-3-hydroxy-5-methyl-4-isoxazole propionate

CaMKII
Ca^{2+}/calmodulin-dependent protein kinase II

CKII
casein kinase II

ER
endoplasmic reticulum

GFP
green fluorescence protein

GRIP
glutamate receptor interacting protein

LTD
long-term depression

LTP
long-term potentiation

MAPK
mitogen-activated protein kinase

mGluR
metabotropic glutamate receptor

NMDA
N-methyl-D-aspartate

PICK-1
protein interacting with C-kinase-1

PDZ
PSD95 discs-large ZO-1

PKA
cAMP-dependent protein kinase

PKC
protein kinase C

PKG
cGMP-dependent protein kinase

PLC
phospholipase C

PP1
protein phosphatase 1

PP2A
protein phosphatase 2A

PP2B
protein phosphatase 2B or calcineurin

PSD
postsynaptic density

PTK
protein tyrosine kinase

PTP
protein tyrosine phosphatase

SAP97
synapse associated protein 97

SAP102
synapse associated protein 102

SH3
Src homology domain 3

STDP
spike-timing dependent plasticity

STEP
striatal enriched tyrosine phosphatase

TARP
transmembrane AMPA receptor regulatory protein

Table 1

Protein kinases and protein phosphatases involved in synaptic plasticity

Protein kinase	Activation	Known synaptic substrates	Proposed role for mediating synaptic plasticity
CaMKII	Increased activity with TBS (Fukunaga et al., 1993). Increased autophosphorylation at T286 with TBS (Barria, Muller et al., 1997). Increased autophosphorylation at T286 in dendrites with HFS (4×100 Hz, 1 sec, ITI=30 sec) (Ouyang et al., 1997).	CaMKII (Lai et al., 1986; Miller & Kennedy, 1986), GluR1 (Barria, Derkach et al., 1997; Mammen et al., 1997), NR2B (Omkumar et al., 1996; Strack et al., 2000), SAP97 (Gardoni et al., 2003; Mauceri et al., 2004), Rabphilin (Fykse et al., 1995), Stargazin (Tomita et al., 2005), Synapsin I (Huttner et al., 1981; Czernik et al., 1987).	E-LTP expression (Malenka et al., 1989; Malinow et al., 1989; Silva et al., 1992; Otmakhov et al., 1997; Lee et al., 2000). CaMKII-alpha autophosphorylation on T286 necessary for LTP (Giese et al., 1998). Metaplasticity (Mayford et al., 1995; Elgersma et al., 2002; Zhang et al., 2005). Homeostatic synaptic plasticity (Thiagarajan et al., 2002).
PKA	Transient activation after HFS (3×100 Hz, 1 sec (ITI=5 sec)) (Roberson & Sweatt, 1996).	GluR1 (Roche et al., 1996), GluR4 (Carvalho et al., 1999), NR1 (Tingley et al., 1997), NR2A (Krupp et al., 2002), Rabphilin (Fykse et al., 1995), Stargazin (Chen et al., 2000; Chetkovich et al., 2002), Synapsin I (Huttner et al., 1981; Czernik et al., 1987).	E-LTP expression (Lee et al., 2000; Otmakhova et al., 2000; Skeberdis et al., 2006). L-LTP expression (Matthies & Reymann, 1993; Huang & Kandel, 1994; Qi et al., 1996; Abel et al., 1997). LTP induction during early development (Yasuda et al., 2003; Wikstrom et al., 2003). “Priming” LTP (Oh et al., 2006). “Gating” LTP (Blitzer et al., 1995, 1998). RII-beta subunit involved in LTD (Brandon et al., 1995).
PKC	Increased membrane bound PKC 30 min after HFS (1×100 Hz, 1 sec) (Sacktor et al., 1993). Increased membrane bound PKC 1 hr after, but not 1 min after HFS (?) (Akers et al., 1986). Decreased activity following LTD induction in vivo (Thiels et al., 2000).	GAP43/Neuromodulin /B-50/F-1 (Aloyo et al., 1983; Akers & Routtenberg, 1985), GluR1 (Roche et al., 1996), GluR2 (Matsuda et al., 1999; Chung et al., 2000; McDonald et al., 2001), GluR4 (Carvalho et al., 1999), MARCKS (Wu et al., 1982; Stumpo et al., 1989), Neurogranin/ RC3 (Baudier et al., 1989), NR1 (Tingley et al., 1997; Sanchez-Perez & Felipo, 2005). NR2B (Liao et al., 2001), Stargazin (Tomita et al., 2005).	LTP maintenance (Lovinger et al., 1987; Kauer et al., 1988; Reymann, Brodemann et al., 1988; Reymann, Frey et al., 1988; Huang et al., 1992). LTP induction (Huang et al., 1992). PKCgamma necessary for LTP, but not for LTD or DeD (Abeliovich et al., 1993).
PKMzeta	Increase in cytosol 30 min after HFS (1×100 Hz, 1 sec) (Sacktor et al., 1993). Decreased in cytosol 30 min after 3 Hz, 5 min stimulation (Hrabetova & Sacktor, 1996).		Maintenance of L-LTP (Sacktor et al., 1993; Ling et al., 2002; Serrano et al., 2005). Maintenance of I-LTP (Serrano et al., 2005). Decreased during LTD maintenance (Hrabetova & Sacktor, 1996).
PKG			LTP expression (Zhuo et al., 1994). L-LTP expression (Lu et al., 1999). Not involved in LTP (Selig et al., 1996). Not necessary for LTP (Kleppisch et al., 1999).
CKII	Transient activation with HFS (2×100 Hz, 0.5 sec (ITI=?)) (Charriaut-Marlangue et al., 1991).	GAP43/Neuromodulin (Pisano et al., 1988; Apel et al., 1991), NR2B (Chung et al., 2004).	LTP expression (Charriaut-Marlangue et al., 1991).
MAPK	Activation of p42 MAPK (ERK2) after HFS (2×100 Hz, 1 sec (ITI=20 sec) repeated 3 times at 10 min intervals) (English & Sweatt, 1996). Increased phosphorylation in dendrites after 5 Hz, 3 sec or 5 Hz, 3 min stimulation (Winder et al., 1999).	Synapsin I (Matsubara et al., 1996).	L-LTP expression (English & Sweatt, 1997). Not involved in LTP maintenance (English & Sweatt, 1997). Regulates LTP induction (Winder et al., 1999). Involvement in LTP depends on induction protocol used (Selcher et al., 2003). ERK1 not necessary for LTP (Selcher et al., 2001).
Tyrosine kinases	Activation of Src with HFS (2×100 Hz, 0.5 sec (ITI=10 sec)) (Lu et al., 1998).	GluR2 (Hayashi & Huganir, 2004), NR2A (Zheng et al., 1998; Vissel et al., 2001; Yang & Leonard, 2001),	LTP induction (O'Dell et al., 1991; Huang & Hsu, 1999; Coussens et al., 2000; Huang et al., 2001). Fyn-

Protein kinase	Activation	Known synaptic substrates	Proposed role for mediating synaptic plasticity
		NR2B (Nakazawa et al., 2001; Prybylowski et al., 2005).	kinase necessary for LTP expression (Grant et al., 1992). Src and Yes kinase not necessary for LTP (Grant et al., 1992). Src activity required for LTP induction (Lu et al., 1998). LTD induction (Coussens et al., 2000).
PP1	Transient increase in activity following *in vivo* LTD induction (Thiels et al., 1998).	PSD associated CaMKII-alpha (Strack, Barban et al., 1997), GluR1 (Kameyama et al., 1998), stargazin (Tomita et al., 2005).	LTD induction (Mulkey et al., 1993). LTD of NMDAR-mediated synaptic transmission (Morishita et al., 2005). Negatively regulates LTP induction (Blitzer et al., 1998; Brown et al., 2000).
PP2A	Persistent increase in activity following *in vivo* LTD induction (Thiels et al., 1998). Decreased activity with TBS (Fukunaga et al., 2000).	Soluble CaMKII-alpha (Strack, Barban et al., 1997), GluR1 (Kameyama et al., 1998).	LTD induction (Mulkey et al., 1993).
PP2B (calcineurin)		GluR1 (Kameyama et al., 1998), NR2A (Krupp et al., 2002), stargazin (Tomita et al., 2005).	LTD induction (Mulkey et al., 1994). Calcineurin-alpha specifically involved in depotentiation, but not LTD (Zhuo et al., 1999). Negatively regulates LTP induction (Winder et al., 1998; Malleret et al., 2001). Involved in E-S potentiation (Lu et al., 2000).

Additional abbreviations: DeD (dedepression: LTD reversal), E-LTP (early phase LTP), ERK (extracellular signal-regulated kinase), E-S potentiation (EPSP to spike potentiation), GAP43 (growth associated protein-43), HFS (high frequency stimulation), I-LTP (intermediate-phase LTP), ITI (inter-train interval), L-LTP (late-phase LTP), MARCKS (myristoylated alanine-rich C-kinase substrate), PKMzeta (protein kinase M zeta), TBS (theta burst stimulation).

Table 2

Phosphorylation sites on NMDA receptor subunits

Subunit	Phosphorylation site	Protein kinase	Function
NR1	S890	PKC (Tingley et al., 1997), PKCgamma (Sanchez-Perez & Felipo, 2005)	Dispersion of surface NR1 (Ehlers et al., 1995; Tingley et al., 1997). Permissive for ER exit (Scott et al., 2003).
	S896	PKC (Tingley et al., 1997), PKCalpha (Sanchez-Perez & Felipo, 2005)	Permissive for ER exit (Scott et al., 2003).
	S897	PKA (Tingley et al., 1997)	Necessary for ER exit (Scott et al., 2003).
NR2A	Y842	Src (Vissel et al., 2001)	Part of YWKL internalization motif (Vissel et al., 2001). Dephosphorylation is responsible for agonist-induced decline in NMDAR current (Vissel et al., 2001). Works together with NR1-Y837 (Vissel et al., 2001).
	S900, S929	PKA (Krupp et al., 2002)	Glycine-independent desensitization of NR1/NR2A channels (Krupp et al., 2002).
	Y1105, Y1267	Src (Zheng et al., 1998)	Potentiates NMDAR current by reducing tonic Zn^{2+} inhibition (Zheng et al., 1998).
	Y1292, Y1325	Src (Yang & Leonard, 2001)	?
	Y1387	Src (Zheng et al., 1998; Yang & Leonard, 2001)	Potentiates NMDAR current by reducing tonic Zn^{2+} inhibition (Zheng et al., 1998).
	S1416	PKC (Gardoni et al., 2001)	Inhibits CaMKIIalpha binding (Gardoni et al., 2001).
NR2B	Y1252, Y1336,	Fyn (Nakazawa et al., 2001)	?
	S1303, S1323	PKC (Liao et al., 2001)	Potentiates channel current (Liao et al., 2001).
	S1303	CaMKII (Omkumar et al., 1996; Strack et al., 2000)	Promotes slow dissociation of CaMKII-NR2B complex (Strack et al., 2000).
	Y1472	Fyn (Nakazawa et al., 2001; Prybylowski et al., 2005)	Part of YEKL internalization motif (Roche et al., 2001; Prybylowski et al., 2005). Stabilizes synaptic NR2B (Roche et al., 2001; Prybylowski et al., 2005). Increase in phosphorylation with LTP (Nakazawa et al., 2001). Dephosphorylation mediates Abeta-dependent endocytosis (Snyder et al., 2005).
	S1480	CKII (Chung et al., 2004)	Part of PDZ ligand domain (ESDV). Inhibits binding to PSD95 and SAP102 (Chung et al., 2004). Decreases surface expression (Chung et al., 2004).

Table 3

Phosphorylation sites on AMPA receptor subunits

Subunit	Phosphorylation site	Protein kinase	Identified functions
GluR1	S818	PKC (Boehm et al., 2006)	Phosphorylation is necessary and sufficient for GluR1 synaptic insertion by LTP (Boehm et al., 2006).
	S831	CaMKII (Barria, Derkach et al., 1997; Mammen et al., 1997), PKC (Roche et al., 1996)	Increases single channel conductance of homomeric receptors (Derkach et al., 1999; Oh & Derkach, 2005). Persistent increase following LTP (Barria, Muller et al., 1997; Lee et al., 2000). Dephosphorylation after depotentiation (Lee et al., 2000). Can substitute for S845 in mediating LTP (Lee et al., 2003; Lee et al., 2004). Homeostatic plasticity (Goel et al., 2006).
	T840	PKC (Lee et al., 2002)	Highly phosphorylated in the hippocampus under basal conditions (Lee et al., 2002).
	S845	PKA (Roche et al., 1996)	Increases mean open probability of channel (Banke et al., 2000). Persistent dephosphorylation following LTD (Kameyama et al., 1998; Lee et al., 1998; Lee et al., 2000; Brown et al., 2005). Necessary for LTD expression (Lee et al., 2003; Lee et al., 2004). Increase in phosphorylation after de-depression (Lee et al., 2000). Necessary for insertion into synapses with LTP induction (Esteban et al., 2003). Can substitute S831 for mediating LTP (Lee et al., 2003; Lee et al., 2004). Regulates AMPA receptor recycling (Ehlers, 2000). Homeostatic plasticity (Goel et al., 2006).
GluR2	Y842	Src (Hayashi & Huganir, 2004)	Phosphorylation decreases binding to GRIP (Hayashi & Huganir, 2004). Phosphorylation is necessary for NMDA-induced internalization (Hayashi & Huganir, 2004).
	S863	PKC (McDonald et al., 2001)	Not been characterized.
	S880	PKC (Matsuda et al., 1999; Chung et al., 2000; McDonald et al., 2001)	Decreases binding to GRIP and favors interaction with PICK1 (Matsuda et al., 1999; Chung et al., 2000). Increases following LTD *in vitro* (Kim et al., 2001). Decreases following LTD *in vivo* (Thiels et al., 2002). Necessary and sufficient for LTD (Seidenman et al., 2003).
GluR4	T830	PKC (Carvalho et al., 1999)	Increases surface expression in heterologous cells (Correia et al., 2003).
	S842	PKA (Carvalho et al., 1999)	Necessary for spontaneous activity-driven synaptic insertion (Esteban et al., 2003).