

Coordination of Protein Phosphorylation and Dephosphorylation in Synaptic Plasticity*

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A central theme in nervous system function is equilibrium: synaptic strengths wax and wane, neuronal firing rates adjust up and down, and neural circuits balance excitation with inhibition. This push/pull regulatory theme carries through to the molecular level at excitatory synapses, where protein function is controlled through phosphorylation and dephosphorylation by kinases and phosphatases. However, these opposing enzymatic activities are only part of the equation as scaffolding interactions and assembly of multi-protein complexes are further required for efficient, localized synaptic signaling. This review will focus on coordination of postsynaptic serine/threonine kinase and phosphatase signaling by scaffold proteins during synaptic plasticity.

Control of Synaptic Strength through Balanced Phosphorylation/Dephosphorylation

A defining aspect of the mammalian brain is its profound capacity for experience-dependent plasticity that modifies the strength of specific synaptic connections between neurons. Two well studied opposing forms of synaptic plasticity at excitatory synapses are long-term potentiation (LTP)² and long-term depression (LTD), which strengthen and weaken synapses, respectively. LTP and LTD have been most heavily studied in a brain region called the hippocampus where they support spatial and declarative learning and memory. LTP and LTD are induced by Ca²⁺ influx through postsynaptic NMDA-

type ionotropic glutamate receptors (NMDARs) and are expressed by long-lasting increases or decreases, respectively, in the function of AMPA-type ionotropic glutamate receptors (AMPA) that mediate the bulk of excitatory synaptic transmission (1, 2).

NMDARs are heterotetrameric assemblies most commonly containing two GluN1 and two GluN2A-2D subunits and are permeable to Na⁺, K⁺, and Ca²⁺. At hippocampal synapses, NMDARs are assembled from GluN1, GluN2A, and GluN2B subunits. AMPARs are heterotetrameric assemblies of GluA1–GluA4 subunits, with most being permeable only to Na⁺ and K⁺ due to inclusion of GluA2 subunits that prevent Ca²⁺ influx (3). However, hippocampal neurons can also express small numbers of Ca²⁺-permeable AMPARs lacking GluA2 subunits (*i.e.* GluA1 homomers) that primarily reside in extrasynaptic and intracellular locations but can be recruited to synapses during plasticity and following neuronal injuries (4). Intriguingly, there is much commonality in the molecular mechanisms underlying the ostensibly antagonistic processes of LTP and LTD; both require correlated pre- and postsynaptic activity leading to NMDAR Ca²⁺ influx and are mediated by overlapping sets of enzymes. However, it is the ability of the synapse to detect subtle differences in Ca²⁺ and other second messengers and efficiently transduce these signals to discrete downstream signaling pathways that permits diametrically opposed outcomes to arise from grossly similar synaptic stimuli.

Ultimately, excitatory synaptic plasticity must add, remove, or modify AMPARs to alter synaptic strength. Although AMPAR regulation during plasticity is covered in-depth elsewhere in this series (see Roche and colleagues (101)), it bears mentioning here. Brief, strong NMDAR Ca²⁺ influx can activate a host of kinases that increase AMPAR activity during LTP through phosphorylating both AMPARs (2, 5–7) and other regulatory proteins (5, 8, 9). AMPAR GluA1 subunits, in particular, are phosphorylated on several C-terminal tail residues to alter channel biophysical properties and synaptic localization. For example, Ca²⁺-calmodulin-dependent protein kinase II (CaMKII) and PKC phosphorylate GluA1 on Ser-831 and Ser-818 (PKC only) to increase single channel conductance and synaptic incorporation during LTP. GluA1 is also phosphorylated on Ser-845 by the cAMP-dependent protein kinase (PKA), which increases channel open probability and stimulates recycling exocytosis to prime AMPARs for synaptic insertion during LTP (reviewed in Refs. 5–7). Thus, although CaMKII may be the most important, direct transducer of NMDAR Ca²⁺ signaling during LTP, multiple postsynaptic kinases collectively promote potentiation (Fig. 1).

Conversely, LTD can be elicited by weak but sustained NMDAR Ca²⁺ influx. Under these conditions, protein phosphatases 1 (PP1), 2A (PP2A), and calcineurin (CaN; also known as PP2B) become activated (10–12) (Fig. 1). Consequently, dephosphorylation of AMPARs as well as other postsynaptic targets is generally favored during LTD. In particular, GluA1 Ser-845 dephosphorylation is critical for AMPAR removal during LTD through promoting endocytosis and preventing recy-

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² The abbreviations used are: LTP, long-term potentiation; LTD, long-term depression; AC, adenylyl cyclase; AKAP, A-kinase anchoring protein; β_2 AR, β_2 -adrenergic receptors; CaM, calmodulin; CaMK, Ca²⁺-calmodulin-dependent protein kinase; CaN, calcineurin; CDK5, cyclin-dependent kinase 5; CREB, Ca²⁺/cAMP-responsive element-binding protein; CRTCI, CREB-regulated transcriptional co-activator; E-T, excitation-transcription; I-1, inhibitor-1; I-2, inhibitor-2; LTCC, L-type calcium channel; NFAT, nuclear factor of activated T-cells; PP1, protein phosphatase 1; PP2A, protein phosphatase 2A; PP2B, protein phosphatase 2B; PSD, postsynaptic density; NMDAR, NMDA-type ionotropic glutamate receptor; AMPAR, AMPA-type ionotropic glutamate receptor.

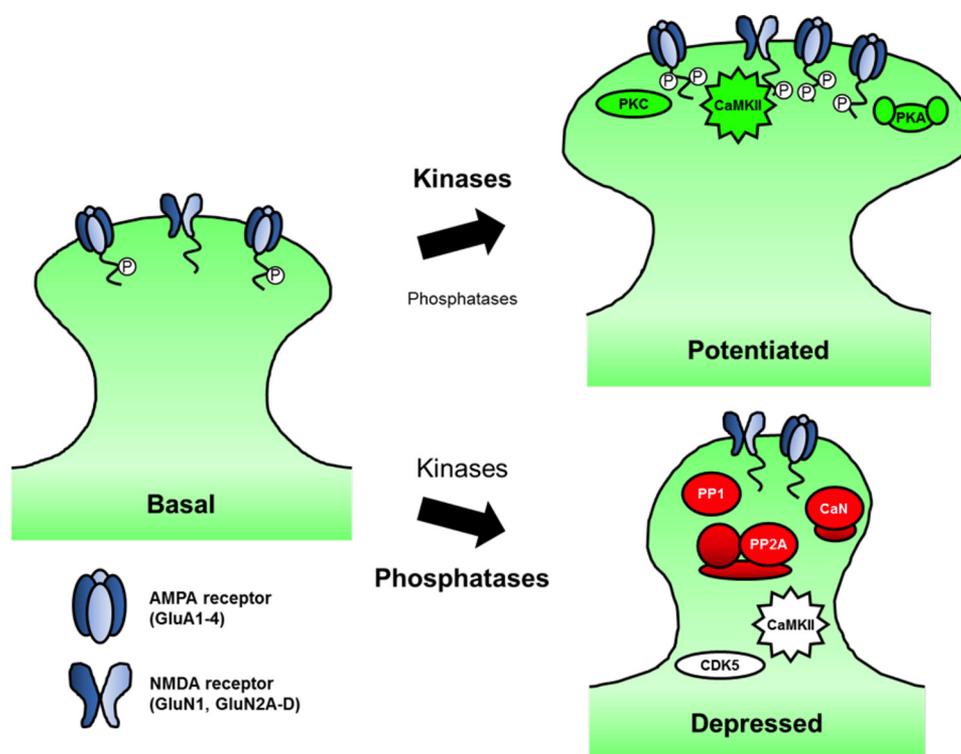


FIGURE 1. **Postsynaptic phosphorylation/dephosphorylation signaling during synaptic plasticity.** During synaptic potentiation, brief, strong cytosolic Ca^{2+} predominantly activates kinases such as CaMKII, PKC, and PKA. AMPA (GluA1–4 subunits) and NMDA-type (GluN1 and GluN2A–2D subunits) glutamate receptors are among the many synaptic targets that are phosphorylated, promoting stronger synaptic transmission. Conversely, during the modest, prolonged influx of Ca^{2+} that initiates synaptic depression, phosphatase activity in general outweighs kinase activity; CaN, PP1, and PP2A dephosphorylate receptors, scaffolds, and other synaptic proteins, resulting in smaller dendritic spines and diminished synaptic strength. However, kinases also play roles in synaptic depression.

cling to favor receptor degradation (reviewed in Refs. 5–7). Because of its direct activation by Ca^{2+} and CaM, CaN is probably the most important, direct transducer of NMDAR Ca^{2+} signaling during LTD, but other phosphatases and kinases, including CaMKII (discussed below), also play essential roles during LTD (Fig. 1). Thus, an overriding question addressed in this review is how are ubiquitous second messenger systems (cAMP and Ca^{2+}) and signaling enzymes with broad substrate specificity (PKA, CaMKII, PP1, and CaN) organized at synapses to coordinate very specific, localized signaling events during LTP and LTD?

Coordinated Regulation of Postsynaptic PKA, PKC, and Calcineurin Signaling by AKAP79/150

Important answers to the above question may be found in the network of scaffolding interactions found in the postsynaptic density (PSD), a structure located at the tip of dendritic spines opposite the presynaptic terminal (see also Spence and Soderling (102) in this issue for more on dendritic spine structure). Scaffold proteins in this PSD network position signaling enzymes to respond to second messengers and exert rapid effects on synaptic substrates. The PKA-PKC-CaN complex assembled by A-kinase anchoring protein (AKAP) 79/150 (human 79/rodent 150; also known as AKAP5) is a prototypical example of a postsynaptic scaffold-organized signaling complex (Fig. 2) (13).

First characterized by its ability to bind PKA through its C-terminal amphipathic α -helical domain (14), AKAP79/150

was subsequently shown to bind CaN (15) through a variant of the PXLIT motif found in other CaN-binding proteins (16–18) and PKC through its N-terminal membrane-targeting domain (19). AKAP79/150 also acts as a structural scaffolding hub as it binds F-actin (20), the plasma membrane lipid phosphatidylinositol-4,5-bisphosphate (21), synaptic adhesion molecules (22), and PSD-95 family scaffold proteins that link to NMDARs and AMPARs (23). Given its collection of anchored enzymes and linkage to glutamate receptors, it is not surprising that AKAP79/150 plays an integral role in synaptic plasticity. Indeed, experiments using AKAP150 knock-out mice demonstrated roles for this scaffold in hippocampal LTD and spatial learning (24). Additional analysis of AKAP150 C-terminal truncation knock-in mice lacking the PKA anchoring site showed more specifically that AKAP-PKA signaling promotes GluA1 Ser-845 phosphorylation and supports LTP, LTD, and reversal learning (25–27). Furthermore, studies employing RNAi with mutant replacement (28, 29) and an AKAP150 knock-in mouse lacking the PXLIT-like CaN docking motif (30) reveal that anchored CaN mediates GluA1 Ser-845 dephosphorylation and AMPAR endocytosis to promote LTD and constrain LTP. In addition, genetic disruption of AKAP-CaN or -PKA anchoring alters spatial and contextual fear learning and memory.³ Finally, although AKAP79/150-anchored PKC can phosphorylate GluA1 Ser-831 in heterologous cells and cultured neurons,

³ M. L. Dell'Acqua, unpublished observations.

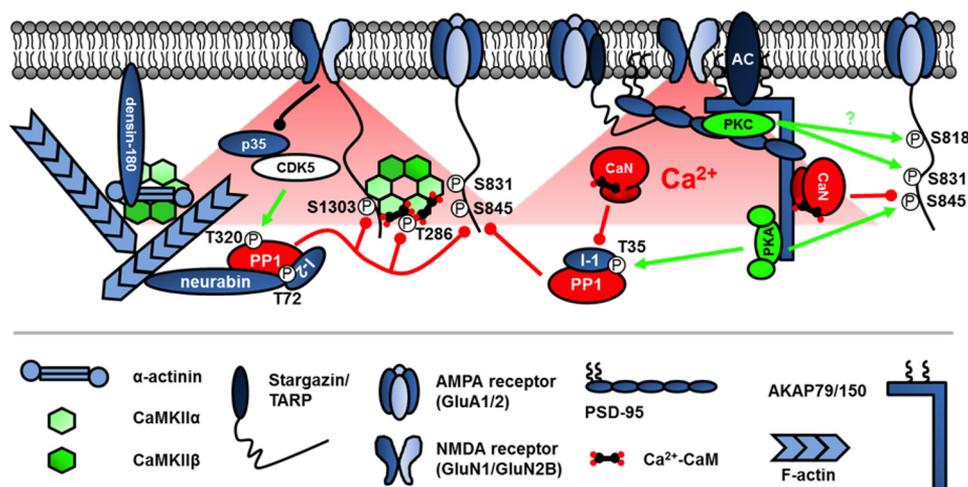


FIGURE 2. Kinase and phosphatase scaffolding is critical for postsynaptic signaling during plasticity. Enzymes are targeted to Ca^{2+} and cAMP sources and important substrates through association with synaptic scaffolds such as AKAP79/150 and PSD-95 as well as actin-binding proteins such as neurabin and α -actinin. CaMKII is unique in that it serves as an enzyme, self-scaffold, and actin organizer. *Circled P* represents phosphorylation. *Green lines* represent phosphorylation, and *red lines* represent dephosphorylation. The *black line* represents degradation of p35 that inactivates CDK5 kinase activity. The specific AMPARs and NMDARs depicted are GluA1/2 and GluN1/2B. TARP is an abbreviation for transmembrane AMPA receptor regulatory protein.

the role of AKAP-PKC anchoring in synaptic plasticity and cognition has not been addressed (31). Taken together, these studies illustrate the critical role that scaffolding can play in locally balancing phosphorylation and dephosphorylation to control synaptic plasticity.

In addition to positioning kinases and phosphatases, AKAPs can bind other key components of the cAMP signaling pathway, including G protein-coupled receptors, adenylyl cyclases (ACs), and phosphodiesterases. AKAP79/150 binds to the β_2 -adrenergic receptor (β_2AR) (32) and multiple AC isoforms (33, 34). β_2AR s couple to AC-cAMP-PKA signaling to enhance LTP and learning and memory through GluA1 phosphorylation (35, 36). In a series of elegant experiments comparing AKAP150 knock-out mice with AKAP150-PKA binding-deficient mice, AKAP knockouts exhibited a greater deficiency in β_2AR enhancement of GluA1 Ser-845 phosphorylation and LTP (37). The less severe phenotype of the PKA binding-deficient mice was attributed to preserved interaction with AC, resulting in normal β_2AR -stimulated cAMP production that likely signaled, albeit less effectively, through other pools of PKA. Of note, AKAP250/Gravin (also known as AKAP12) can also associate with β_2AR s to facilitate LTP regulation (38). Thus, there is likely interplay between these two AKAP-PKA complexes in postsynaptic LTP regulation. Interestingly, in many of the above studies, AKAP79/150-anchored PKA and CaN were found to impact LTP/LTD through preferential control of GluA1 Ca^{2+} -permeable AMPARs, perhaps because these GluA1 homomers can be phosphorylated on four Ser-845 sites as compared with only two in GluA1/2 heteromers (26, 30, 37).

Due to their micrometer size, dendritic spines themselves are microdomains for compartmentalized signaling, but it is clear that AKAP79/150 and other PSD scaffold proteins nucleate postsynaptic signaling complexes that function on the molecular/nanometer scale. Such intra-spine nano-domain signaling may occur near receptors in the PSD, in extrasynaptic regions of the spine plasma membrane, or in spine-localized endo-

somes. AKAP79/150 also serves as an excellent example of postsynaptic nano-targeting, as its own localization is fine-tuned by reversible palmitoylation of its N-terminal targeting domain by the palmitoyl-acyltransferase DHHC2 (39, 40). AKAP79/150 palmitoylation is not required for general targeting to the plasma membrane but is necessary for specific localization to plasma membrane lipid rafts (which are associated with the PSD) and recycling endosomes (40, 41). Importantly, AKAP79/150 palmitoylation in endosomes is required for stimulation of recycling exocytosis and delivery of the AKAP and GluA1 to synapses during chemical LTP induction (39, 40). However, in general, our understanding of the trafficking of AKAP79/150 and other postsynaptic scaffolds lags behind our understanding of the AMPAR trafficking that they control. We do know that AKAP79/150 can be uncoupled from PSD-95 scaffolds and removed from both the postsynaptic membrane and the endosomes during chemical LTD induction through inhibition of its N-terminal targeting interactions via a combination of depalmitoylation (39), phospholipase C cleavage of phosphatidylinositol-4,5-bisphosphate, and CaN-dependent F-actin reorganization. Importantly, this inhibition of AKAP79/150 membrane targeting during LTD may prevent PKA-mediated re-phosphorylation of GluA1 that would promote recycling and reverse LTD (reviewed in Ref. 13). Interestingly, changes in AKAP79/150 synaptic localization, PKA and CaN signaling, and GluA1 Ser-845 phosphorylation have also recently been implicated in regulating GluA1 synaptic localization during slower, homeostatic forms of synaptic plasticity that scale synaptic strength up or down across all inputs in response to chronic increases or decreases in overall neuronal activity, respectively (42, 43).

Regulation of Postsynaptic CaMKII Signaling

CaMKII is dodecameric holoenzyme assembled from α , β , γ , and δ isoforms. In most neurons, CaMKII contains $\alpha > \beta \gg \gamma/\delta$ isoforms. Due to its enrichment at synapses and mechanisms of Ca^{2+} regulation, CaMKII (α in particular) has

attracted substantial attention in the synaptic plasticity field (44–46). In response to Ca^{2+} elevation, Ca^{2+} -CaM binding to CaMKII displaces the autoinhibitory domains to permit active site access for both exogenous substrates and Thr-286 (Thr-287 on β , γ , δ) in the autoinhibitory domain of neighboring Ca^{2+} -CaM-bound subunits. Autophosphorylation of Thr-286 modifies CaMKII function in two ways: it enhances Ca^{2+} -CaM binding affinity (so-called CaM trapping) and prevents the autoinhibitory domain from fully occupying the active site, generating what is referred to as CaMKII “autonomy” wherein the kinase remains partially active after CaM dissociation. Importantly, CaMKII autonomy functions as a form of “molecular memory” of past Ca^{2+} signals and plays crucial roles in both LTP induction and learning and memory (47, 48). CaMKII Thr-286 can be dephosphorylated by either PP1 or PP2A, but PP1 appears to play a more prominent role in dephosphorylation of CaMKII in the PSD (49). Following strong synaptic stimulation, more CaMKII is also rapidly recruited to the PSD (50–53), where it phosphorylates not only AMPARs and its auxiliary subunits (8, 9) but also small GTPase regulators (54, 55) and adhesion molecules (56). With so many important targets, how is CaMKII postsynaptic signaling controlled? Because there are a number of comprehensive reviews on this topic (44–46), here we will primarily focus on specific postsynaptic scaffolding interactions that control CaMKII signaling (Fig. 2).

The CaMKII holoenzyme configuration permits CaMKII α and β subunits to serve as scaffolds for one another through both common and distinct interacting proteins. F-actin binding is one such interaction that is distinctly controlled by β versus α subunits. CaMKII can associate indirectly with F-actin through the adapter protein α -actinin (57) but can also bind F-actin directly through its β isoform (58–61). Upon activation by Ca^{2+} -CaM, CaMKII β unbinds from F-actin, allowing the kinase to redistribute and establish new interactions. In particular, CaMKII activation promotes binding to the PSD scaffold densin-180; however, because densin-180 also binds α -actinin, a ternary complex results that can still be linked to F-actin but also further associate with NMDARs through CaMKII binding to GluN2B subunit (57, 62, 63). However, adding to this complexity, there are secondary interactions of CaMKII with the GluN1 subunit that are instead inhibited by α -actinin binding to GluN1 (64). Importantly, CaMKII and F-actin have reciprocal effects on one another; CaMKII is positioned by its interactions with F-actin but in turn can directly bundle and stabilize actin fibers through its β isoform in a Ca^{2+} -CaM-regulated manner (59–61). Indeed, CaMKII β is important for the integrity of the actin cytoskeleton, and its loss destabilizes spines (61). Interestingly, this effect of CaMKII β loss on spines can be rescued with a kinase-inactive mutant, highlighting the function of CaMKII as a structural scaffold. The importance of this kinase-independent role is further supported by comparing the phenotypes of CaMKII β knock-out mice with those expressing kinase-inactive CaMKII β (65). Although CaMKII β knock-out impairs CaMKII synaptic localization, LTP, and learning, none of these functions are disrupted by the kinase-inactive mutation.

As alluded to above, another key CaMKII postsynaptic interaction is with the NMDAR GluN2B subunit, which contains a

binding site in its C-terminal tail near the CaMKII phosphorylation site Ser-1303 (66–69). Recruitment of activated CaMKII to GluN2B occurs rapidly following Ca^{2+} stimulation but, like Thr-286 phosphorylation, outlasts the Ca^{2+} signal, thus permitting postsynaptic CaMKII to participate in yet another form of “molecular memory.” Indeed, CaMKII binding to GluN2B has been implicated in LTP maintenance and memory consolidation. In one study, a high dose of an inhibitor peptide (tatCN21), which competes with GluN2B for CaMKII binding, was found to acutely disrupt both GluN2B-CaMKII binding and LTP maintenance (70). In a second study, CaMKII binding-deficient GluN2B knock-in mice exhibited reductions in GluA1 Ser-831 phosphorylation, LTP, and memory consolidation (71). Collectively, these findings support a model in which CaMKII enzymatic and non-enzymatic functions may work together to process and store information at excitatory synapses.

Abundant evidence exists for the role of CaMKII in LTP, but there is accumulating evidence that it also participates in LTD (72). Intriguingly, a newly characterized Ser-567 phospho-site in GluA1, which results in AMPAR synaptic exclusion (73), was recently shown to be phosphorylated by autonomous CaMKII under NMDAR LTD conditions (72). In addition, GluA1 Ser-567 exhibits distinct characteristics as compared with typical CaMKII substrates implicated in LTP (*i.e.* Ser-831) in that Ca^{2+} -CaM stimulation does not elevate Ser-567 phospho-levels above those obtained with autonomous CaMKII. Thus, an intriguing new hypothesis is that there are two classes of CaMKII substrates that are differentially regulated by stimulated versus autonomous kinase activity to favor either LTP or LTD, respectively. These recent findings also provide a clear exception to the over-simplified rule that kinases mediate synaptic potentiation and phosphatases mediate synaptic depression.

Regulation of Postsynaptic PP1 Signaling

Another challenge in understanding plasticity is that synaptic changes are often controlled through multiple parallel and overlapping signaling pathways, such as CaN, PP1, and PP2A phosphatases that all participate in LTD (10–12). Like control of CaN signaling by AKAP79/150, PP1 and PP2A signaling also rely heavily on binding partners to regulate activity and subcellular targeting, but because less is known about regulation of PP2A signaling during LTD, here we will only discuss PP1. Prominent among postsynaptic PP1 regulatory proteins are the related F-actin-binding proteins neurabin-1 (Fig. 2) and spinophilin (also called neurabin-2), which anchor PP1 through modular binding motifs with the loose consensus sequence (K/R)(V/I)X(F/W) that is commonly abbreviated as RVXF (74). Importantly, disruption of the interaction between PP1 and neurabin/spinophilin using competing RVXF binding motif peptides can block LTD (75). In addition, specific interference with neurabin-PP1 association by mutation inhibits LTD, whereas overexpression of wild-type neurabin-1 enhances LTD and promotes dephosphorylation of GluA1 Ser-845 and Ser-831 (76, 77). Overall, these findings support a model where neurabin-1 recruits PP1 to synapses to promote AMPAR dephosphorylation during LTD.

Thus, another key question is how is PP1 enzymatic activity regulated by synaptic activity when complexed with scaffolds such as neurabin? Historically, models for NMDAR activation of PP1 during hippocampal LTD have implicated CaN-mediated dephosphorylation of PP1 inhibitory PKA substrate inhibitor-1 (I-1) (10). Also, PKA phosphorylation of neurabin-1 can inhibit its PP1 binding, a mechanism that may favor LTP (76, 78). However, several additional PP1 regulatory mechanisms have recently received attention in NMDAR signaling, including PP1 binding to inhibitor-2 (I-2), possibly in a ternary complex with neurabin-1, and PP1 inhibitory phosphorylation on Thr-320. In particular, recent work identified cyclin-dependent kinase 5 (CDK5) as the kinase for PP1 Thr-320 and demonstrated that when CDK5 is inhibited by synaptic NMDAR activation via proteasomal degradation of its p35 subunit, PP1 auto-dephosphorylates to become active (79). This study also uncovered a requirement for association of PP1 with I-2, which was increased by I-2 Thr-72 dephosphorylation, to promote PP1 signaling during NMDAR LTD; this mechanism stands in contrast with reversal of PP1 association with I-1 through Thr-35 dephosphorylation. Collectively, these studies indicate that a kinase (CDK5) and multiple PP1-binding proteins conspire to regulate postsynaptic PP1 activity (Fig. 2). Interestingly, another recent study found that PP1 is also required for homeostatic synaptic downscaling, but in this case, PP1 is activated by release from I-2 inhibition through Ser-43 phosphorylation by myosin light-chain kinase (80).

Coordinated Kinase and Phosphatase Signaling in Postsynaptic Excitation-Transcription Coupling

Longer-lasting forms of plasticity that are maintained for hours, days, months, or even years, such as the late phase of LTP, require not only initial changes in AMPAR synaptic localization that occur during the early-phase of LTP but also subsequent gene transcription (81) and protein synthesis (covered by Alvarez-Castelao and Schuman (103) in this issue). Several pathways linking acute changes in neuronal activity to persistent alterations in gene transcription rely on local Ca^{2+} influx through voltage-gated L-type calcium channels (LTCCs) to trigger phosphorylation or dephosphorylation of transcription factors, such as Ca^{2+} /cAMP-responsive element-binding protein (CREB), CREB-regulated transcriptional coactivator (CRTC1), and nuclear factor of activated T-cells (NFAT) (82–84). In particular, a privileged role for LTCC Ca^{2+} signaling to CREB in neuronal excitation-transcription (E-T) coupling associated with LTP/LTD and long-term memory has been known for almost 25 years (85–88).

The transcriptional activating function of CREB itself can be controlled by phosphorylation on Ser-133 by a variety of kinases including PKA, CaMKs, and ERK (81). However, studies of E-T coupling have revealed vital roles for not only kinases but also phosphatases in activating CREB-dependent transcription. In a variety of neuron types, LTCCs activate both CaN and CaMKII, which can have either opposing or cooperative roles in regulating CREB-mediated transcription (83, 89, 90). However, recent studies in sympathetic and cortical neurons found that LTCC Ca^{2+} influx recruits CaMKII β to the channel to transphosphorylate Thr-287 in the autoinhibitory domain of

CaMKII γ and promote Ca^{2+} -CaM trapping, whereas concomitant activation of CaN dephosphorylates Ser-334 in a nuclear localization sequence on CaMKII γ . Subsequent CaMKII γ translocation and shuttling of CaM to the nucleus then activates CaMK kinase (CaMKK) and CaMKIV to phosphorylate CREB (91). Interestingly, a kinase-inactive mutant of CaMKII γ , which could not phosphorylate itself or other substrates but still served as substrate for CaMKII β , was able to signal to CREB, thus providing additional support for a CaM shuttling rather than an enzymatic role for CaMKII γ . Thus, phosphorylation of CaMKII γ at two critical sites allows it to shuttle CaM to the nucleus and induce gene transcription. However, the molecular details of how changes in CaMKII γ phosphorylation state and CaM binding are so precisely regulated to only load CaM at the channel and then release it in the nucleus await further investigation. In addition, according to this mechanism, only CaMKII holoenzymes exclusively composed of the γ isoform must be able to enter the nucleus (Fig. 3); otherwise it is hard to rule out additional signaling by enzymatically active CaMKII β that enters the nucleus in association with CaMKII γ .

The above CaMKII-CaMKIV signaling mechanism also likely contributes only to an initial, rapid phase of CREB activation (seconds to minutes) following excitation where Ca^{2+} increases not only near LTCCs but also globally to maintain Ca^{2+} -bound CaM all the way to the nucleus. In contrast, more prolonged CREB activation (minutes to hours) in response to local LTP induction and restricted Ca^{2+} influx in dendrites is thought to be mediated by local, postsynaptic CaMKII activation of the ERK pathway followed by slower, longer-distance translocation of ERK signaling from dendrites to nucleus to phosphorylate CREB (87, 92, 93). In addition, the CREB co-activator CRTC1 is dephosphorylated by CaN in response to LTCC Ca^{2+} influx triggered by synaptic input to dendrites and then also slowly translocates distally to the nucleus where it is required for CREB-dependent gene expression underlying fear memory (83, 94). Thus, although many key players in CREB E-T coupling have been identified, future work must further explore the mechanisms of cellular and synaptic organization that permit signaling to CREB over these different distance and time scales.

A parallel E-T coupling system, in which more has already been learned regarding the contribution of postsynaptic organization to nuclear signaling, is NFAT translocation to the nucleus (over minutes to an hour) following brief, local LTCC Ca^{2+} influx in neurons. Work over the past decade has revealed the complexity and importance of an AKAP79/150-organized signaling complex in both PKA/CaN bi-directional regulation of neuronal LTCC activity and NFAT-mediated E-T coupling (Fig. 3) (18, 95, 96). AKAP79/150 directly binds the LTCC $\text{Ca}_v1.2$ through a C-terminal leucine zipper and anchors CaN through a PXLIT-like motif that is very similar to the CaN docking sequences found in the NFAT transcription factors themselves (17). However, despite essentially competing with NFAT for CaN binding and also suppressing PKA-mediated enhancement of LTCC activity, AKAP79/150-CaN anchoring is critical for NFAT activation by LTCC Ca^{2+} influx (18, 95). How exactly is LTCC-CaN-NFAT signaling promoted by the AKAP? Guided by the crystal structure of the AKAP-CaN com-

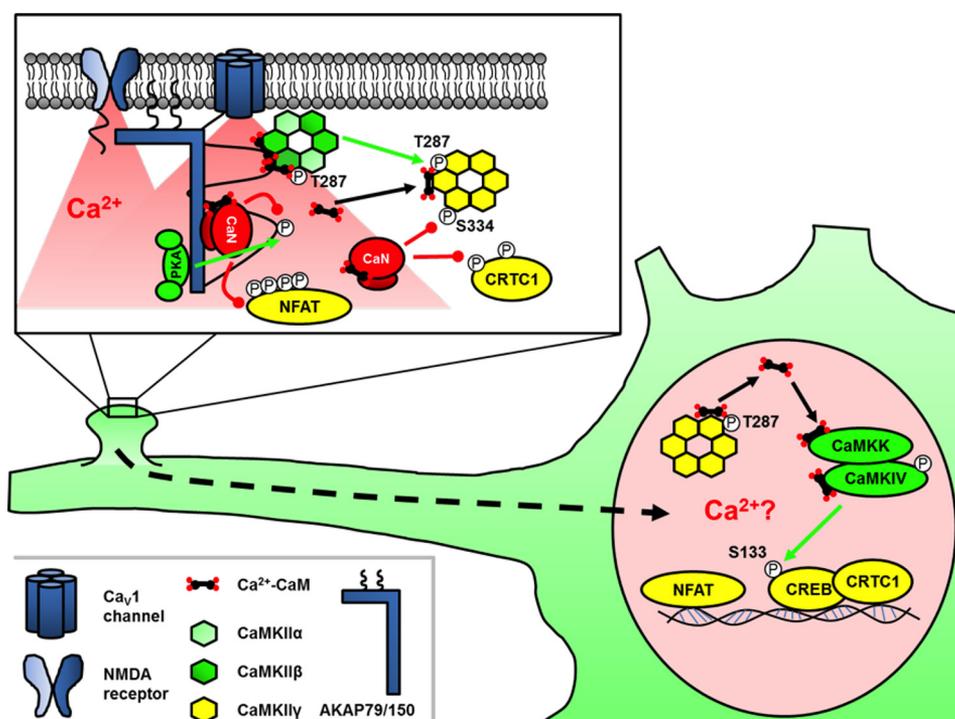


FIGURE 3. **Signaling by kinases and phosphatases in postsynaptic excitation-transcription coupling.** Anchored kinases and phosphatases finely tune Ca^{2+} influx through LTCCs. The calcium-activated phosphatase CaN dephosphorylates nuclear localization sequences on the transcription factors NFAT and CRTTC1, permitting their translocation to the nucleus. LTCC-calcium influx also activates CaMKII α/β that can phosphorylate and “lock” CaMKII γ in a conformation that tightly binds Ca^{2+} -CaM. Subsequent CaN-mediated dephosphorylation of the nuclear localization sequence of CaMKII γ drives nuclear translocation and delivery of Ca^{2+} -CaM to CaMKIV, which phosphorylates and activates CREB. Green lines represent phosphorylation, and red lines represent dephosphorylation.

plex, mutations in the PXLIT-like motif designed to either increase or decrease CaN anchoring affinity, were both, surprisingly, found to inhibit NFAT activation. In particular, increasing anchoring affinity immobilized CaN in spines and prevented NFAT translocation to the nucleus (97). Thus, AKAP-CaN anchoring is by necessity dynamic and promotes NFAT signaling by balancing strong recruitment of CaN near its upstream activator, the LTCC, with its efficient release to communicate with its downstream effector NFAT.

Building on this theme of dynamics and balance in local signaling complexes, additional research found that disruption of AKAP79/150-PKA anchoring, both through acute overexpression and through knock-in of PKA anchoring-deficient mutants, also prevents NFAT signaling, a deficit attributable to profound decreases in basal LTCC phosphorylation, current density, and depolarization-evoked Ca^{2+} influx (98, 99). Thus, neuronal LTCC-NFAT transcriptional signaling requires precise organization and balancing of the phosphatase activity of CaN in the channel nano-environment, which is required for NFAT activation, with the opposing kinase activity of PKA, which is needed to prevent CaN from suppressing channel function. Importantly, these studies of AKAP79/150 provide some of the most complete and detailed molecular mechanisms to date explaining how local Ca^{2+} signaling by LTCC plays such a privileged role in neuronal E-T coupling.

Conclusions and Future Directions

It is clear that postsynaptic kinase/phosphatase signaling balance is key to synaptic plasticity regulation on multiple

time scales through controlling both local signal transduction confined to synapses as well as distal communication with the nucleus. In all cases, the high degree of signaling specificity and efficiency required is conferred by regulatory binding partners/scaffolds that are as important as the activities of the kinases and phosphatases themselves in determining impacts on synaptic function. Indeed, distinct and even opposing types of plasticity can involve the same kinase and phosphatase players, but the actions of these players appear to be directed by scaffolding interactions toward one pathway or another to achieve different outcomes. Future research should further elucidate how scaffold proteins play key roles in such local, postsynaptic decision making through interrogating signaling complexes on the nanometer scale using new super-resolution microscopy methods (100). In addition, it will be important to further explore how scaffold-directed phosphorylation intersects with signaling through other reversible post-translational modifications, such as palmitoylation and ubiquitination (6)(see also Alvarez-Castelao and Schuman (103) in this issue). Finally, given that many neuropsychiatric and neurological disorders are characterized by alterations in synaptic plasticity, a better understanding of how kinase/phosphatase signaling pathways are organized at synapses will hopefully identify novel drug targets and therapies for brain diseases. Precisely targeting synaptic scaffolding interactions could have many advantages, in terms of improved efficacy and specificity, over globally inhibiting kinase and phosphatase catalytic activity using existing pharmacology.

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