Chapter 5
PKA Anchoring and Synaptic Tagging and Capture

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Abstract Synaptic tagging and capture (STC) hypothesis has been receiving increasing attention because it reflects heterosynaptic association of information processing during memory formation in the brain. Indeed, electrophysiological and behavioral studies suggest that STC is a better cellular model for memory formation than the conventional homosynaptic experiment. In STC, a short-lasting potentiation in one pathway becomes persistent when it is paired with a long-lasting potentiation in the other independent pathway. It has been proposed that the setting of synapse-specific tag and capture of non-synapse-specific diffusible gene products by the tag determines the fate of each pathway. However, the mechanism of STC is still elusive and three major questions should be answered: (1) What is the tag and how does it modulate synapse-specific plasticity? (2) How does the tag capture gene products? (3) What are the gene products and how are they produced? Although several molecules and processes have been suggested to answer to these questions, they only provide partial explanations about the phenomenon. Here, this article will discuss how PKA modulates synapse-specific neuronal processing by coordinating signaling molecules and processes through PKA anchoring proteins, and how anchored PKA is involved in the generation and capture of plasticity-related gene products. Having PKA as a key molecule, the goal of this article is to provide a unified model of STC that addresses the key questions.

Keywords cAMP • PKA • AKAP • PKA anchoring • Synaptic tagging and capture

5.1 Introduction

Synaptic plasticity, the activity-dependent change in synaptic strength, has been extensively studied as a cellular/physiological correlate of memory storage (Mayford et al. 2012). Memory is stored in the hippocampus, and physiological and behavioral studies have been conducted to unravel the mechanism of memory processes

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in this brain area. Hippocampal long-term potentiation (LTP) has been studied as the primary model for memory storage because of its long duration, input specificity, and associativity (Bliss and Gardner-Medwin 1973; Bliss and Lomo 1973). The hippocampal Schaffer collateral—CA1 region is an output area of the hippocampus to the cortex, and damage to CA1 impairs memory formation (Zola-Morgan et al. 1986; Auer et al. 1989). Various forms of synaptic plasticity in CA1 have distinct molecular requirements. Early-LTP (E-LTP), the neural correlate of short-term memory (STM), lasts 1–2 h and requires NMDA receptor and Ca^{2+}/calmodulin-dependent protein kinases II (CaMKII) activation, but does not require PKA activation, transcription, and protein synthesis (Huang and Kandel 1994; Tsien et al. 1996). In contrast, late-LTP (L-LTP), the neural correlate of long-term memory (LTM), lasts several hours and requires PKA activation, transcription, and protein synthesis in addition to NMDA receptor and CaMKII activation (Frey et al. 1996, 1988; Huang and Kandel 1994; Nguyen et al. 1994; Tsien et al. 1996; Nguyen and Kandel 1997; Abel et al. 1997; Matsushita et al. 2001; Otmakhov et al. 2004). As with L-LTP, studies of hippocampus-dependent behavioral tasks also demonstrate that PKA activation, transcription, and protein synthesis are critical determinants discriminating STM from LTM formation (Barondes and Jarvik 1964; Abel et al. 1997; Pittenger and Kandel 1998; Meiri and Rosenblum 1998).

These findings provide critical groundwork to understand the mechanisms underlying L-LTP and LTM. However, studies on homosynaptic LTP recordings and LTM from a single behavioral experience using naïve animals have substantial limitations because they do not reflect the complex nature of memory processing that requires integration of multiple synaptic inputs from several interacting experiences. Memory formation is continuously influenced by past, present, and future experiences. Memories linked to events that require more attention or involve emotional arousal are more persistent than ordinary memories (Richter-Levin and Akirav 2003). To account for this complex memory processing, a synaptic model addressing integration of multiple inputs is needed. Synaptic tagging and capture (STC), first described in rodent hippocampal CA1 and *Aplysia* neurons in 1997 (Frey and Morris 1997; Martin et al. 1997), demonstrates the association and integration of synaptic activities of two independent sets of synapses. Frey and Morris placed two stimulating electrodes on either side of a recording electrode in the hippocampal area CA1 in order to stimulate two independent sets of synapses that were converging onto the same population of CA1 neurons (Fig. 5.1a). In this experiment, they showed that weak stimulation-induced E-LTP in one pathway became persistent when the weak pathway was paired with strong stimulation-induced L-LTP in the other pathway. According to the STC hypothesis, strong stimulation (S1) not only *tags* the activated synapses, but also *induces* production of gene products (Plasticity Related Products, PRPs). These tagged synapses then *capture* the gene products that migrate within the neurons. The capture of PRPs by the tag allows L-LTP expression in the S1 pathway (Fig. 5.1b). On the contrary, weak stimulation (S2) only generates tags, and therefore L-LTP is not induced because PRPs are not available for the tag to capture (Fig. 5.1c). However, once this S2 pathway is paired with the S1 pathway, the tag in the S2 pathway can capture PRPs produced from the S1 pathway and thereby transform E-LTP to L-LTP in the S2 pathway (Fig. 5.1d). Input specificity described by

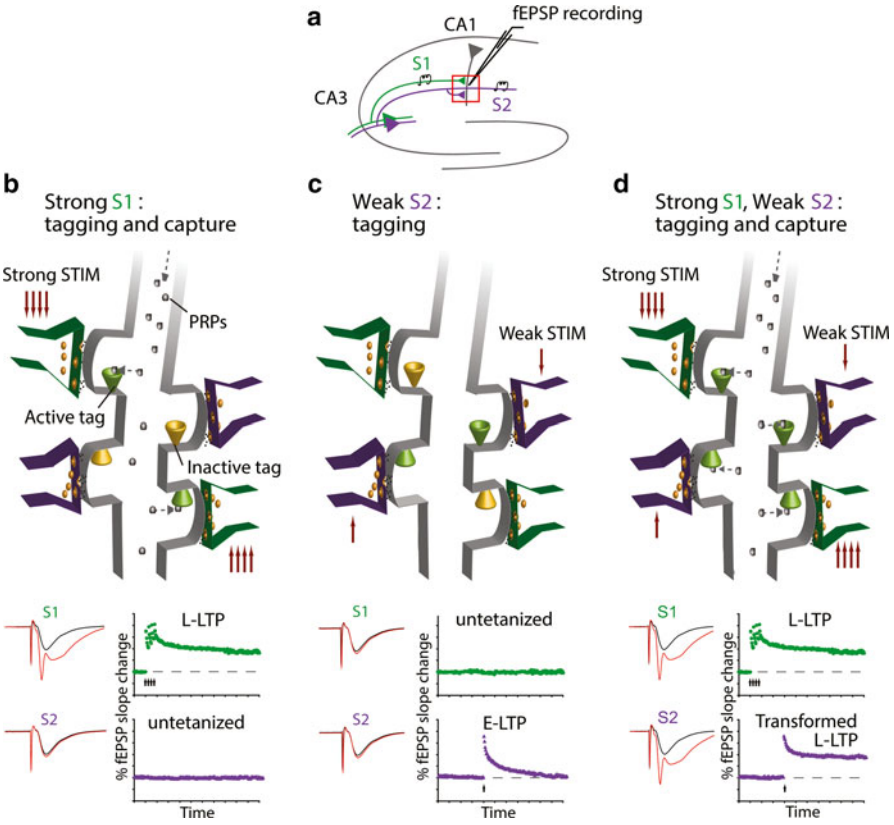

Fig. 5.1 Synaptic tagging and capture. (**a**) Schematic diagram of the two-pathway experiment. Two stimulating electrodes are positioned to stimulate two independent pathways (S1 and S2) converging onto the same CA1 neurons. (**b**) A strong stimulation activates local tags and induces PRP production. The capture of PRPs by the activated tags allows L-LTP expression in the S1 pathway. (**c**) A weak stimulation only activates local tags and induces E-LTP in the S2 pathway. (**d**) Pairing of S1 and S2 pathways results in capture of PRPs from the S1 pathway by activated tags in the S2 pathway which transforms E-LTP to L-LTP in the S2 pathway. Left lower insets are representative traces (*black*: baseline, *red*: hours after stimulation), and right lower insets are representative slope recordings of field excitatory postsynaptic potentials (fEPSP) over hours. (Modified with permission from Ted Huang, Ph.D.)

STC is efficient in that the tagged synapses can use the same pool of PRPs produced by the strong stimulation. The time window or the duration of the tag, which allows for successful L-LTP capture, is about 1–2 h (Frey and Morris 1998). Behaviorally, weak task-induced STM can also become long-lasting by a strong independent task that produces protein synthesis-dependent LTM (Moncada and Viola 2007; Ballarini et al. 2009; Wang et al. 2010b). Hence, heterosynaptic capture and the longer period of associativity described by STC provide a better representation of the complex integrative nature of memory processing.

Although STC has been studied by many researchers over the last decade, the identity of the tag remains elusive. The tagging process is the most critical component of STC because PRP production alone is not sufficient for L-LTP expression (Barco et al. 2002). Lines of evidence suggest multiple requirements for being a tag. A tag should be (1) spatially restricted to activated synapses, (2) transient and reversible, (3) interacting with PRPs, and (4) independent of protein synthesis (Martin and Kosik 2002; Kelleher et al. 2004b). As many molecules and processes (e.g. NMDA receptor, PKA, CaMKII, TrkB, actin polymerization, etc.) have been independently proposed as tags (Martin and Kosik 2002; Redondo and Morris 2011), tagging likely involves the coordination of multiple molecules or processes rather than a single molecule or a single process. Kinase-mediated processes are the strongest candidate tagging mechanisms. By reversible phosphorylation of their targets, kinases provide a history of activated synapses. The most convincing evidence supporting this idea is that low frequency stimulation (LFS) resets tags and this tag-reset is mediated by increased phosphatase activities. Also, LFS-induced detagging does not affect already established STC and gene expression (Barco et al. 2002; Sajikumar and Frey 2004; Young and Nguyen 2005; Young et al. 2006). More importantly, increased phosphatase activities by LFS interfere with PKA activity (Young et al. 2006). If PKA is the central molecule coordinating tagging processes, the next question that arises is how such a diffusible molecule can modulate spatially restricted STC processes. In fact, PKA signaling is highly localized by a family of scaffold proteins known as A-kinase-anchoring proteins (AKAPs) (Michel and Scott 2002). In this article, we will discuss PKA as a key tagging molecule that modulates proposed tagging mechanisms and how AKAPs compartmentalize PKA and its targets to ensure synapse-specific tagging processes.

5.2 The Role of PKA in Synaptic Plasticity and Memory Formation

In the brain, the heterosynaptic neuromodulatory system is critical for information processing, and likely a deterministic factor making memory long-lasting. Major neuromodulators in the brain are the dopaminergic, adrenergic, and serotonergic systems. These neuromodulators project to various brain regions, including the hippocampus. At the synaptic level, they may modulate L-LTP by lowering the threshold for tag setting or PRP production (Richter-Levin and Akirav 2003). Dopaminergic and noradrenergic signaling not only modulate electrically induced L-LTP but also facilitate L-LTP and STC expression (Frey et al. 1991; Gelinas and Nguyen 2005; Gelinas et al. 2008; Connor et al. 2011; Havekes et al. 2012). Interestingly, these modulatory innervations are linked to G-protein coupled receptors (GPCRs). Upon ligand binding, GPCRs activate adenylate cyclases (ACs) to produce the ubiquitous secondary messenger, cAMP. Targets of cAMP are PKA, exchange proteins directly activated by cAMP (Epac), and the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. Although Epac and HCN channels are involved in regulation

of the neuronal function, their roles in synaptic plasticity and memory are less well understood (Laurent et al. 2012; Benarroch 2013). As a major target of cAMP, the role of PKA in L-LTP and LTM has been extensively studied. Mice expressing a dominant negative PKA regulatory subunit have significantly reduced L-LTP in the area CA1 and exhibit deficits in hippocampus-dependent memory (Abel et al. 1997). The PKA inhibitors Rp-cAMP and KT5720 block L-LTP (Matthies and Reymann 1993; Frey et al. 1993), and PKA activation mediates a form of L-LTP facilitated by β-adrenergic receptor activation in the area CA1 (Gelinas et al. 2008). Additionally, PKA activation by dopaminergic innervations is involved in LTM formation, and pharmacological activation of PKA enhances LTM formation as well as L-LTP expression (Bernabeu et al. 1997; Barad et al. 1998). In the next section, we will expand our knowledge on the contribution of PKA to synaptic plasticity by providing evidence that supports the role of PKA in STC.

5.3 The Requirement for PKA in Synaptic Tagging and Capture

The most compelling evidence for PKA as a critical molecule for L-LTP is that direct activation of PKA by pharmacological agents such as Sp-cAMP (a cAMP analog), forskolin (FSK, adenylate cyclase activator that enhances cAMP production), and inhibitors of phosphodiesterases (PDE, cAMP degrading enzyme) successfully induces transcription- and protein synthesis-dependent long-lasting potentiation which occludes electrically induced L-LTP (Frey et al. 1993; Huang and Kandel 1994; Slack and Walsh 1995; Abel et al. 1997; Selbach et al. 1998; Woo et al. 2002). The fact that PKA activation itself is sufficient for L-LTP expression strongly suggests that PKA mediates tagging and capture processes. Indeed, PKA is required for STC. PKA inhibitor KT5720 treatment and expression of a dominant negative PKA regulatory subunit impair STC (Young et al. 2006). PKA activation by a PDE inhibitor, caffeine facilitates STC (Sajikumar et al. 2009). Also, PDE4 inhibitor, rolipram augments protein synthesis-dependent L-LTP and STC (Navakkode et al. 2004). Moreover, LFS activates phosphatases that resets tagging by dephosphorylation of PKA targets (Sajikumar and Frey 2004; Young et al. 2006). In line with this, inhibition of protein phosphatase 1 (PP1) by PKA is critical for L-LTP expression, and PP1 inhibitors rescues L-LTP deficits in mice expressing a dominant negative PKA regulatory subunit (Blitzer et al. 1998; Woo et al. 2002). Importantly, PKA inhibitors are effective only when they are treated during the induction phase of STC (Barco et al. 2002; Young et al. 2006). This transient involvement of PKA in STC complies with the requirement for being a tag molecule (see Sect. 5.1). However, PKA is not the only tag molecule that has been proposed, and we will discuss how PKA interacts with other candidate tagging mechanisms in the next section.

5.4 Other Potential Tagging Mechanisms Possibly Mediated by PKA

NMDA Receptors (NMDARs) are required for L-LTP and LTM (Morris et al. 1986; Nguyen and Woo 2003). The NMDAR has been suggested as a tagging molecule because the NMDAR inhibitor AP5 blocks STC, although PRPs are still available for being captured (Barco et al. 2002). It is worth noting that Ca^{2+}-influx through NMDARs activates Ca^{2+}-dependent ACs, which results in the activation of PKA. Also, increased Ca^{2+} permeability of the NMDAR by PKA phosphorylation facilitates LTP (Skeberdis et al. 2006). Therefore PKA, at least in part, mediates tagging processes involving NMDARs.

CaMKII is activated by Ca^{2+}-influx through NMDARs after LTP induction, and is another strong candidate tag molecule. Pharmacological inhibition of CaMKII blocks STC, providing evidence that STC requires CaMKII. Also, inhibition of CaMKII does not affect PRP production and subsequent capture of PRPs (Redondo et al. 2010). Following NMDAR stimulation, an active form of CaMKII moves to the postsynaptic density (PSD) of activated dendritic spines, then phosphorylates its targets (Shen and Meyer 1999). Because PKA modulates NMDAR-mediated Ca^{2+} signaling, it is likely that PKA and CaMKII act in concert in the process of tagging. Indeed, it has been reported that inhibition of PP1 by PKA gates CaMKII signaling by preventing dephosphorylation of CaMKII during L-LTP expression (Blitzer et al. 1998). However, the role of CaMKII as a tag is not clear. Unlike PKA phosphorylation of AMPA receptor (AMPAR) subunit GluR1 at S845, CaMKII-mediated phosphorylation of GluR1 at S831 does not increase open probability of the receptor (Banke et al. 2000). In addition, a GFP reporter flanked by the 5′- and 3′-UTR of CaMKII shows local dendritic synthesis after stimulation, and the protein level of CaMKII increases in dendrites within 5 min after tetanization (Ouyang et al. 1999; Aakalu et al. 2001). Dendritic local synthesis of CaMKII does not comply with the criteria for being a tag, since the tagging process is independent of protein synthesis. Therefore, CaMKII is possibly a component of PRPs.

TrkB is a tyrosine kinase that has been suggested as a potential tag. Its ligand is brain-derived neurotrophic factor (BDNF), which will be discussed later as a strong candidate PRP (see Sect. 5.5). Bath application of BDNF induces protein synthesis-dependent long-lasting potentiation, suggesting that BDNF-TrkB signaling is sufficient to elicit tagging and capture processes as PKA activation does (Kang et al. 1996; Messaoudi et al. 2002). Inhibition of TrkB blocks STC and a behavioral version of tagging, and TrkB activation after stimulation lasts about 1–2 h. Also, TrkB activation does not require protein synthesis (Lu et al. 2011). Therefore, TrkB satisfies the requirements for a tag. In fact, PKA activation gates BDNF-induced TrkB phosphorylation (Ji et al. 2005). In addition, TrkB phosphorylation is increased after PKA activation by forskolin (Patterson et al. 2001). This suggests that PKA is upstream of BDNF-TrkB signaling and that the described roles of TrkB as a tag are likely modulated by PKA.

Actin Dynamics are important for the structural modification of synapses and memory formation (Krucker et al. 2000; Lisman 2003; Chen et al. 2007; Hou et al. 2009). NMDAR-dependent actin polymerization in dendritic spines is critical for L-LTP (Lin et al. 2005), and BDNF signaling modulates this process (Rex et al. 2007). LFS reverses LTP by depolymerizing actin (Kramár et al. 2006). Moreover, inhibition of actin polymerization impairs tagging process but does not affect PRP production (Ramachandran and Frey 2009). Actin remodeling is controlled by cofilin, an actin depolymerizing factor. Cofilin-mediated actin dynamics regulate spine morphology and AMPAR trafficking during synaptic plasticity (Chen et al. 2007; Gu et al. 2010). Phosphorylation of cofilin by LIM kinase inhibits its activity, which allows actin polymerization. In fact, the activity of LIM kinase is modulated by PKA (Lamprecht and LeDoux 2004; Nadella et al. 2009).

5.5 Plasticity-Related Products

As a tag, PKA interacts with plasticity-related products (PRPs) by regulating the synthesis and function of these gene products. PRPs are produced from gene transcription and protein synthesis after neuronal activity. While it was initially believed that only proteins produced in the soma serve as PRPs, it is now widely accepted that mRNAs also serve as PRPs by its dendritic targeting and subsequent local dendritic translation. mRNAs packaged in RNA granules are transported close to synapses in a translationally silent state (Mayford et al. 1996; Krichevsky and Kosik 2001; Wang et al. 2010a). Upon LTP induction, polyribosomes and local translation machinery at spine necks are activated to translate these locally targeted mRNAs (Steward and Schuman 2001; Ostroff et al. 2002; Kelleher et al. 2004b).

PKA activates the transcription factor cAMP response element (CRE)-binding protein (CREB) to promote CRE-driven gene expression critical for both L-LTP and LTM (Impey et al. 1996, 1998b). In addition, CREB-dependent gene expression facilitates synaptic plasticity including STC in both *Aplysia* and mice (Martin et al. 1997; Casadio et al. 1999; Barco et al. 2002). Thus, CREB-mediated CRE-driven gene expression provides a pool of PRPs critical for both L-LTP and LTM. Infusion of PKA inhibitor into the nucleus blocks CREB phosphorylation and impairs L-LTP, but not E-LTP (Matsushita et al. 2001). PKA facilitates nuclear translocation of extracellular-signal-regulated protein kinase (ERK), which leads to CREB phosphorylation (Impey et al. 1998a; Roberson et al. 1999; Patterson et al. 2001). Therefore, PKA directly and indirectly activates CREB. In addition to nuclear gene transcription, translation of mRNAs contributes to PRP production. Dendritic protein synthesis is mainly controlled by mitogen-activated protein kinase (MAPK), BDNF-TrkB signaling pathways, and actin dynamics (Kelleher et al. 2004a; Kuczewski et al. 2010; Santos et al. 2010). PKA cross-talks with the MAPK pathway at multiple levels (Gerits et al. 2008) and modulates BDNF-TrkB signaling and actin dynamics as described earlier (see Sect. 5.4). Collectively, PKA attributes to PRP production both at the level of transcription and protein synthesis.

As a CREB target gene, BDNF has been proposed as the strongest candidate PRP (Tao et al. 1998; Barco et al. 2005). Activity-dependent dendritic targeting and expression of BDNF and TrkB support this idea (Tongiorgi et al. 1997). BDNF promotes synaptic remodeling through actin dynamics, PSD reconstitution, and local translation during L-LTP (Kang and Schuman 1996; Liao et al. 2007; Rex et al. 2007; Yoshii and Constantine-Paton 2007). Additionally, BDNF deletion in the hippocampus impairs STC (Barco et al. 2005). These observations suggest multiple roles of BDNF such that it is not only produced as a PRP but also induces production of other PRPs and aids tag setting, all of which are modulated by PKA (also see Sect. 5.4 TrkB).

Another well-known candidate PRP is the AMPAR. AMPAR trafficking and incorporation into synapses that are regulated by both actin and PKA are critical for L-LTP expression (Malinow et al. 2000; Sheng and Lee 2001; Esteban et al. 2003). PKA phosphorylation at S845 of GluR1 promotes an increase in open probability, frequency, and duration of the receptor that leads to stable LTP expression (Greengard et al. 1991; Banke et al. 2000; Esteban et al. 2003). Although AMPARs can be considered as tags, since their activity and incorporation make synapses more excitable, they are more likely PRPs because their requirement for synaptic plasticity is not transient and their synthesis is required for their rapid turnover. Indeed, the maintenance phase of LTP requires a PKA-mediated increase in AMPAR synthesis 3 h after LTP induction (Nayak et al. 1998; Yao et al. 2008). Taken together, PKA regulates the property, trafficking, as well as synthesis of AMPARs to ensure L-LTP expression.

5.6 The Role of PKA Anchoring in Synaptic Plasticity and Memory Formation

In the previous sections, we discussed PKA as a key molecule mediating the processes of STC, in which synaptic inputs from the two independent pathways (S1 and S2) are integrated. This pathway-specificity is a unique property of neuronal communication that can only be achieved by highly compartmentalized and spatially restricted cellular signaling. This is surprising because secondary messengers including cAMP, kinases such as PKA, mRNAs, and many proteins are diffusible throughout the cell. This suggests that there is a way to localize signaling molecules together to ensure spatially restricted signaling. Spatially compartmentalized PKA signaling is achieved by PKA anchoring proteins, or AKAPs. There are more than 50 AKAPs that are localized to specific intracellular regions. By binding PKA regulatory subunits as well as other signaling molecules, AKAPs provide a compartmentalized pool of PKA signaling (Colledge and Scott 1999; Michel and Scott 2002). The importance of the compartmentalized PKA signaling in synaptic plasticity and memory formation is confirmed by pharmacological and genetic disruption of PKA anchoring by the PKA anchoring disrupting peptide Ht31. This peptide is derived from the human thyroid anchoring protein that binds PKA and has been used to block anchoring of PKA without affecting PKA activity (Colledge and Scott 1999).

Conditional expression of Ht31 in neurons within the hippocampus impairs hippocampal L-LTP and hippocampus-dependent spatial memory, and reduces GluR1 S845 phosphorylation (Nie et al. 2007; Kim et al. 2011). Similar to PKA, the application of Ht31 peptide at different time point reveals that PKA anchoring is transiently required for L-LTP, not E-LTP, and STC during the induction phase (Huang et al. 2006; Havekes et al. 2012). In addition, PKA anchoring disruption by Ht31 reduces synaptic AMPARs and AMPAR currents and occludes long-term depression (LTD) (Rosenmund et al. 1994; Snyder et al. 2005). It should be noted that the effect of Ht31 directly matches the effect of PKA inhibition in synaptic plasticity and memory formation (see Sects. 5.2 and 5.3). This suggests that PKA exerts its activity through anchored signaling complexes controlled by AKAPs.

5.7 Examples of AKAPs Modulating Neuronal Function

In the brain, several AKAPs have been identified as scaffold proteins that tie PKA signaling to Ca^{2+} signaling, MAPK signaling, cytoskeletal dynamics, and gene expression mechanisms. Therefore, AKAPs contribute to the formation of highly coordinated signalosomes that are critical for synaptic plasticity and neuronal information processing.

AKAP5/79/150 is targeted to the plasma membrane and associated with PSD-95. It recruits NMDARs, AMPARs, $GABA_A$ receptors, L-type Ca^{2+} channels, K^+ channels, synapse-associated protein (SAP)-97, PKC, protein phosphatase 2B (PP2B or calcineurin), β-adrenergic receptors (β-ARs), as well as PKA (Bregman et al. 1989; Carr et al. 1992; Coghlan et al. 1995; Gao et al. 1997; Fraser et al. 2000; Colledge et al. 2000; Gomez et al. 2002; Brandon et al. 2003; Hoshi et al. 2003). Deletion of AKAP5/79/150 leads to impaired synaptic plasticity, altered AMPAR currents, and disrupted hippocampus-dependent spatial memory. AKAP5/79/150 also mediates nuclear PKA signaling, and perturbation of PKA anchoring reduces nuclear CREB phosphorylation (Feliciello et al. 1996, 1997).

Gravin (*AKAP12/250*), also known as Src-suppressed C kinase substrate (SSecks) in mice, binds not only PKA but also other signaling molecules including PKC, calmodulin, PP2B, β-ARs, actin, and PDE4D (Lin et al. 1996; Nauert et al. 1997; Shih et al. 1999; Lin and Gelman 2002; Willoughby et al. 2006). By bringing PDEs close to ACs, Gravin provides cAMP gradients to shape compartmentalized PKA signaling. Gravin is also localized to the actin cytoskeleton and regulates actin remodeling (Lin et al. 1996; Gelman et al. 1998). Its localization to the plasma membrane, the endoplasmic reticulum, and the perinuclear region has also been reported (Streb et al. 2004). Along with AKAP 5/79/150, it mediates PKA phosphorylation of β-ARs that leads to desensitization of the receptor and activation of the MAPK pathway (Daaka et al. 1997; Baillie et al. 2003). Mice lacking the α-isoform of Gravin show impaired PKA-dependent L-LTP, β-AR-mediated metaplasticity, and hippocampus-dependent contextual fear memory, possibly due to reduced phosphorylation of β-ARs and MAPK (Havekes et al. 2012). Interestingly, FSK-mediated long-lasting potentiation is not affected in these mice, suggesting

that the cellwide activation of PKA overcomes compartmentalization barriers or that the presence of other AKAPs is sufficient to support this form of potentiation (Havekes et al. 2012).

Microtubule-Associated Protein 2 (MAP2) is the first identified AKAP. As a predominantly expressed AKAP in the brain, MAP2 binds a third of neuronal PKA, and regulates microtubule stabilization and long-distance transport along dendrites and axons (Theurkauf and Vallee 1982; Sánchez et al. 2000). As a dominant AKAP, MAP2 establishes a pool of PKA along dendritic shafts so that, upon cAMP elevation, catalytic subunits of PKA can rapidly translocate to dendritic spines for synaptic plasticity (Zhong et al. 2009). In addition, loss of MAP2 results in reduction of the total amount of PKA and CREB phosphorylation (Harada et al. 2002). The latter suggests MAP2-mediated synapse-to-nucleus signaling of PKA. Deletion of the PKA binding site of MAP2 results in abnormal CA1 architecture and disruption of contextual fear memory (Khuchua et al. 2003). Also, MAP2 mRNA is the first mRNA found to be targeted to dendrites for subsequent local synthesis of the protein (Garner et al. 1988; Steward and Halpain 1999).

5.8 PKA-Centric Unified Model of Synaptic Tagging and Capture

Since first being described in 1997, a large number of studies have proposed various molecules and processes as the mechanisms of synaptic tagging and capture. Although the identity of tagging and capture processes is still elusive, it is likely the collective interaction of molecules, rather than a single molecule, that accounts for these processes. Considering the crucial role of PKA in synaptic plasticity and memory formation, a AKAP-mediated compartmentalized pool of signaling complexes could contribute to the heterosynaptic nature of information processing in the brain, here represented as STC.

When a set of synapses receives supra-threshold stimulation, Ca^{2+}-influx through NMDARs and activation of neuromodulatory GPCRs trigger a large increase of cAMP production by ACs. Following the cAMP wave, a large amount of PKA is activated from both the reserve pool in the dendritic shafts maintained by MAP2 and the local pool maintained by AKAPs in the spine. Activated dendritic PKA then enters the activated spine and interacts with NMDARs, AMPARs, TrkB, and Ca^{2+} signaling cascades in concert with locally activated PKA in the spine (tagging). Having a reserve pool in dendritic shafts is an efficient way to supply PKA to activated synapses on demand. PKA from this reserve pool promotes gene transcription by activating CREB in the nucleus. Also, the cross-talk between PKA and MAPK signaling initiates protein synthesis to produce PRPs such as BDNF. PKA gates subsequent BDNF-TrkB signaling to augment protein synthesis and synaptic remodeling. In addition, PKA regulates AMPAR trafficking via actin dynamics (capture). AKAPs tightly regulate all of these processes by clustering signaling components so that stable L-LTP in this set of synapses is ensured (Fig. 5.2a).

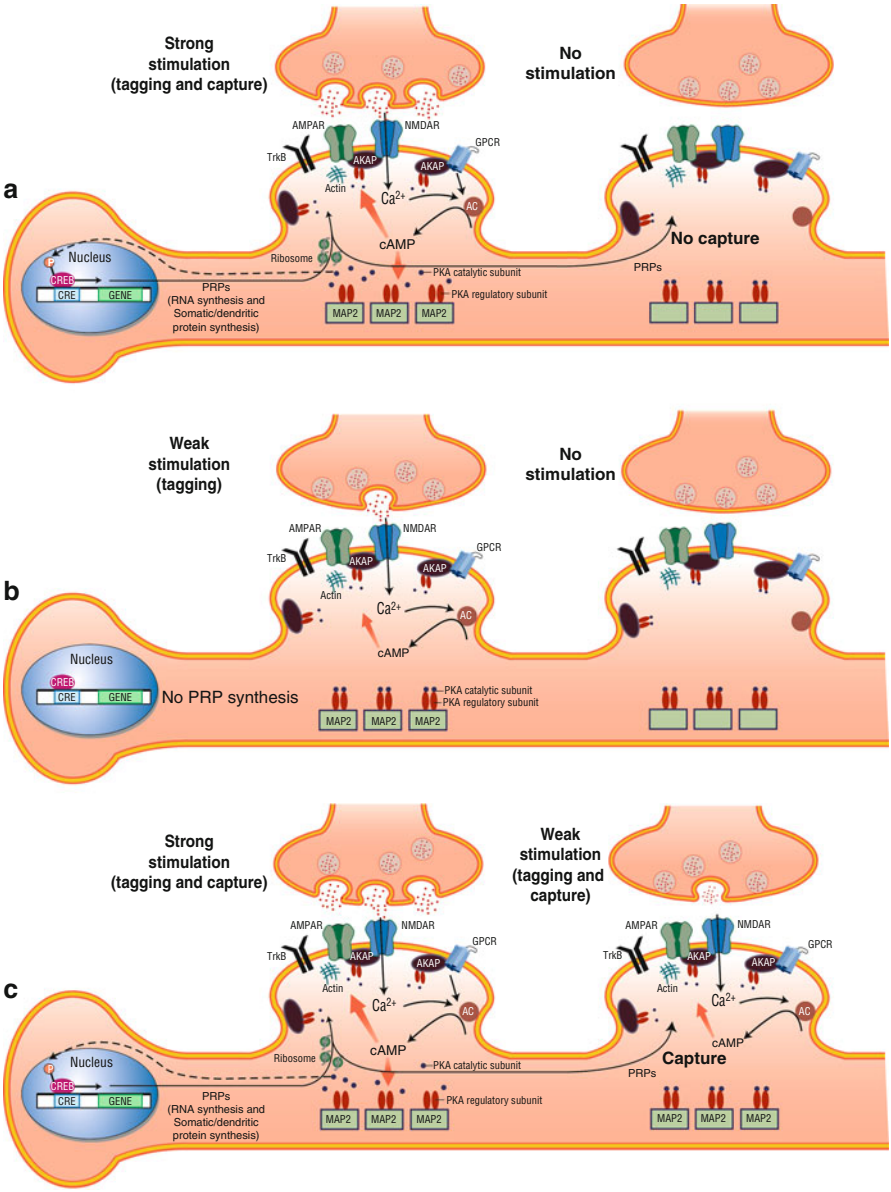

Fig. 5.2 A PKA-centric model of synaptic tagging and capture. (**a**) In the strong pathway, a large amount of cAMP is produced by ACs through NMDAR- and GPCR-mediated processes, which in turn activates PKA from both the local AKAP pool in the spine and the dendritic MAP2 pool. Once activated, PKA catalytic subunits are liberated from PKA regulatory subunits to induce CREB-mediated gene expression and somatic/dendritic protein synthesis to produce PRPs, as well as tagging the activated synapses by priming molecules in the spine (e.g. NMDARs, AMPARs, and TrkB). Upon arrival of PRPs into the spine, only the tagged synapses interact with/capture PRPs (possibly through AMPAR trafficking or BDNF-TrkB signaling) to strengthen the pathway. (**b**) The weak pathway has a sub-threshold level of cAMP produced by NMDAR-mediated Ca^{2+}-dependent AC activation resulting in local activation of PKA only in the spine, which establishes tags in the synapses but does not induce PRP production. (**c**) The weak pathway is strengthened if PRPs from the strong pathway are captured by the tags when the two pathways are paired

When a set of synapses receives sub-threshold stimulation, the amount of activated PKA is not sufficient to induce PRP production, and E-LTP is induced. PKA bound to only local AKAPs tags the set of synapses by priming synaptic proteins such as NMDARs, AMPARs, and TrkB (Fig. 5.2b). If this E-LTP pathway is paired with the L-LTP pathway, PRPs produced by the L-LTP pathway can be captured by the E-LTP pathway, so that E-LTP is transformed to L-LTP. For example, BDNF produced by the L-LTP pathway can strengthen synaptic connection of the weak pathway by interacting with the *primed* signaling molecules such as TrkB (Fig. 5.2c).

In summary, PKA activation through NMDAR activity alone can only set tags at a subset of synapses by priming local targets such as NMDARs, AMPARs, and TrkB. PKA phosphorylation of these targets fades over time, which creates a limited time window of tagging. However, PKA activation through both NMDARs and neuromodulatory GPCRs triggers PRP production as well as local tag setting. PKA-mediated capture processes involve the interaction of PRPs with their signaling partners that have already been primed by PKA (e.g. BDNF-TrkB signaling gated by PKA). Finally, AKAP supervises the heterosynaptic coordination of complex signaling by tethering signaling participants together at the synapse.

5.9 Future Directions

Most of the literature included in this chapter focuses on the postsynaptic mechanisms of STC. Due to technical challenges, it is hard to assess potential presynaptic components of STC. However, there is evidence supporting the presynaptic role of PKA activity and PKA anchoring in L-LTP and memory formation. Long-lasting potentiations induced by Sp-cAMP or FSK relies on increased presynaptic transmitter release (Chavez-Noriega and Stevens 1994; Bolshakov et al. 1997). Additionally, studies using transgenic mice expressing Ht31 suggest that presynaptic CA3-PKA anchoring is required for theta-burst L-LTP and spatial memory (Nie et al. 2007). Moreover, the induction of theta-burst L-LTP increases the release of BDNF as well as synaptic vesicles from presynaptic terminals (Zakharenko et al. 2003). Also, BDNF deletion in both CA3 and CA1 results in complete impairment of STC, while BDNF deletion in only postsynaptic CA1 has a delayed impairment suggesting that BDNF in presynaptic CA3 has a role in the early phase of STC (Barco et al. 2005). To investigate the presynaptic role of PKA and PKA anchoring in STC, genetic approaches specifically blocking PKA anchoring or PKA activity in presynaptic CA3 will be necessary.

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