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Review

Orchestration of synaptic plasticity through AKAP signaling complexes

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Abstract

Significant progress has been made toward understanding the mechanisms by which organisms learn from experiences and how those experiences are translated into memories. Advances in molecular, electrophysiological and genetic technologies have permitted great strides in identifying biochemical and structural changes that occur at synapses during processes that are thought to underlie learning and memory. Cellular events that generate the second messenger cyclic AMP (cAMP) and activate protein kinase A (PKA) have been linked to synaptic plasticity and long-term memory. In this review we will focus on the role of PKA in synaptic plasticity and discuss how the compartmentalization of PKA through its association with A-Kinase Anchoring Proteins (AKAPs) affect PKA function in this process.

Keywords: cAMP-dependent Protein Kinase (PKA); A-Kinase Anchoring Protein (AKAP); cAMP; Neuron; Synaptic plasticity; Learning and memory

1. Introduction: LTD and LTP in memory

How does the brain store and access memory? One current hypothesis is that memories are formed and stored through a process known as ''synaptic plasticity''. This process refers to a lasting up- or down-regulation of synaptic strength following the activation of a synapse (Martin and Morris, 2002). These long-lasting changes in synaptic function are believed to provide, at least in part, the cellular basis of learning and memory (Hebb, 1949; Alkon and Nelson, 1990; Bliss and Collingridge, 1993; Kandel, 1997; Martin et al., 2000). The alterations in synaptic function that result from acute changes in these intracellular signaling cascades correlate with fluctuations in the transcription and translation of target genes. Over the years, great efforts have been placed on studying mechanisms of synaptic plasticity and how these synaptic events relate to memory.

Perhaps the best-studied forms of synaptic plasticity are NMDA receptor-dependent long-term potentiation (LTP) and long term depression (LTD) in the hippocampus. However, it is clear that both NMDA-dependent and NMDA-independent forms of synaptic plasticity also occur in other brain regions (Morris, 1990; Linden et al., 1991; Tsien et al., 1996; Abel et al., 1997; Rogan et al., 1997). LTP is the process whereby brief high frequency stimulation of a neural pathway can induce long lasting increases in the synaptic response (Bliss and Lomo, 1973; Martin and Morris, 2002). Conversely, LTD refers to a long lasting decrease or weakening of synaptic strength elicited by sustained, low frequency, stimulation (Martin et al., 2000). Whether these models of plasticity represent the cellular basis for memory remains controversial, however, a significant body of evidence suggests that the molecular mechanisms underlying these processes are important for learning. For example, in the hippocampus, NMDA receptors have been shown to be critical for one form of LTP. Pharmacological blockade of NMDA receptors prevents the induction of LTP and impairs the performance of mice behavioral models for

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hippocampal-dependent spatial learning such as the Morris water maze task (Bliss and Lomo, 1973; Morris et al., 1986; Davis et al., 1992). Moreover, transgenic mice harboring deletions of two subunits of the NMDA receptor exhibit deficits in LTP and spatial learning (Sakimura et al., 1995; Kew et al., 2000), stressing the importance of these receptors in synaptic plasticity.

Several forms of LTP and LTD have been shown to require the activation of kinases and phosphatases. The calcium/calmodulin-dependent kinase II (CamKII) is a key component of the molecular machinery that underlies LTP in the CA1 region of the hippocampus (Lisman et al., 2002). Induction of LTP increases the CaMKII-dependent-phosphorylation of AMPA receptors (Barria et al., 1997) whereas inhibitors of CaMKII block the induction of LTP (Malenka et al., 1989; Malinow et al., 1989). Furthermore, the perfusion of a constitutively active CaMKII into neurons occludes the induction of LTP (Lledo et al., 1995) highlighting the role of CaMKII in LTP.

Other broad specificity kinases such as protein kinase A (PKA) and protein kinase C (PKC) have been shown to phosphorylate AMPA receptors and regulate channel activity. For example, phosphorylation of AMPA receptors by PKA increases channel activity by increasing the open state probability of the channel (Banke et al., 2000; Lee et al., 2003). In addition, the intracellular application of peptides that inhibit PKA by disrupting its association with anchoring proteins, reduce AMPA-mediated currents, indicating that anchoring of PKA is important in regulating AMPA receptor activity (Rosenmund et al., 1994). The role of PKA in synaptic plasticity will be discussed in greater detail below. PKC also has been shown to phosphorylate AMPA receptors in the hippocampus and increase channel activity (Wang et al., 1994; Song and Huganir, 2002). Interestingly, in the cerebellum, studies in brain slices and cell culture indicate that PKC phosphorylation is the critical kinase for the formation of LTD in the cerebellum emphasizing differences in the mechanisms underlying plasticity in various brain regions (Linden and Connor, 1991; Hartell, 1994; Crepel, 1998; De Zeeuw et al., 1998; Freeman et al., 1998).

Protein phosphatases also have been implicated in the induction of hippocampal LTD. The addition of phosphatase inhibitor proteins, such as Inhibitor 1 (I1), or pharmacological blockers, such as okadaic acid and cyclosporine, block LTD formation (Mulkey et al., 1994; Winder and Sweatt, 2001) suggesting that protein phosphatase I (PP1) and calcineurin (PP2B) may be involved in this process. In fact, a considerable body of evidence suggests that a PP2B/PP1 phosphatase cascade plays a role in the production of LTD (Mulkey et al., 1994; Barria et al., 1997; Lee et al., 2000; Morishita et al., 2001; Winder and Sweatt, 2001). More recently, it has been suggested that PP2B may directly regulate AMPA receptor phosphorylation and synaptic activity (Gomez et al., 2002; Tavalin et al., 2002).

Analysis of transgenic and knockout mice has provided additional evidence for a role of kinases and phosphatases in learning and memory. Mice lacking the CaMKIIα isoform, the most abundant isoform in the hippocampus, display a loss of hippocampal LTP and are severely impaired in their ability to perform in spatial memory tasks (Silva et al., 1992a; Silva et al., 1992b; Silva et al., 1992c). The use of transgenic mice also stressed the importance of the phosphatase PP2B in synaptic plasticity. Mice lacking the regulatory subunit of PP2B exhibit diminished LTD and altered LTP as well as impairments in hippocampal-dependent working and episodic-like memory tasks (Zeng et al., 2001). Interestingly, over expression of PP2B in the forebrain also leads to impairments in hippocampal LTP and defects in spatial memory (Mansuy et al., 1998; Winder et al., 1998) suggesting that there is a fine balance in the level of enzyme activity required for the production of LTP. Although the action of PKA is clearly implicated in the process of learning and memory, its precise role is not completely understood. Mice lacking individual PKA subunit isoforms have been shown to display various defects in LTP/LTD in the hippocampus (Brandon et al., 1995; Huang et al., 1995; Qi et al., 1996). However, future work on the knockout mice is necessary to help determine whether individual PKA subunits play specific roles in memory. Although much remains to be learned about the role of PKA in synaptic plasticity and learning and memory, clearly PKA is one of the signaling molecules involved in these processes and will be discussed further below.

2. PKA and its role in synaptic plasticity

cAMP is a soluble second messenger expressed in all cell types. Phosphorylation mediated by the cAMP signaling pathway can be elicited by number of different ligands such as neurotransmitters, hormones and growth factors. In addition to synaptic plasticity, cAMP signaling also critically regulates other cellular functions including cell motility, growth, metabolism, and ion channel conductivity (Scott, 1991; Francis and Corbin, 1994). The effect of cAMP is primarily mediated through its target, the cAMP-dependent protein kinase (PKA) (Krebs and Beavo, 1979). PKA is composed of two distinct subunits—a regulatory (R) and a catalytic (C) subunit—that form a tetrameric holoenzyme R2C2. In the presence of cAMP, the holoenzyme dissociates to free active C kinase subunits. These active subunits phosphorylate a diverse number of target proteins in the cytoplasm and nucleus (Scott, 1991; Skalhegg and Tasken, 2000), including the transcrip-

tion factor CREB, which binds to DNA regulatory elements such as CRE (cAMP response element) (Dash et al., 1990; Karin and Smeal, 1992; Chrivia et al., 1993) and regulates gene transcription.

Results from genetic screens suggest that signaling through the cAMP pathway is in some way involved in learning and memory. In the 1970's genetic screens carried out in Drosophila looked for mutations that affect learning and memory. The original screen identified the dunce mutant, which contains a mutation in the gene encoding the phosphodiesterase responsible for degrading cAMP (Dudai et al., 1976; Chen et al., 1986). Since then, several groups have conducted screens and have identified other learning and memory mutants that contain mutations in cAMP signaling pathway such as rutabaga and amnesiac which encode for a Ca2+/calmodulin-dependent adenylate cyclase and a gene that is homologous to a pituitary peptide that activates adenylate cyclase, respectively (Dudai et al., 1976; Dubnau and Tully, 1998; Mayford and Kandel, 1999). In addition, flies that express a catalytically inactive form of PKA exhibit deficiencies in olfactory memory strengthening the role for PKA in this process (Drain et al., 1991; Mayford and Kandel, 1999). Additional studies in the marine invertebrate *Aplysia* support a role for PKA in learning and memory. *Aplysia* undergo forms of synaptic plasticity similar to LTP called short- and long-term facilitation (LTF) (Castellucci et al., 1970; Frost and Katz, 1996; Mayford and Kandel, 1999). Decades of research have demonstrated that the processes underlying short- and long-term facilitation in *Aplysia* require a persistently active PKA. This appears to be achieved by the ubiquitin-dependent degradation of the PKA regulatory subunit, which produces a constitutively active catalytic subunit (Greenberg et al., 1987; Chain et al., 1999) and the phosphorylation of activators and repressors of the cAMP response element-binding protein (CREB) (Dash et al., 1990; Bacskai et al., 1993; Kaang et al., 1993; Bartsch et al., 1995, 1998; Chain et al., 1999).

PKA signaling pathways also regulate synaptic plasticity in the mammalian hippocampus. It has been proposed that one mechanism by which PKA can regulate LTP is by modulating the activity of CaMKII (Blitzer et al., 1998; Brown et al., 2000). However, another hypothesis suggests that that PKA may regulate synaptic plasticity by altering the surface expression of AMPA-type glutamate receptors. It has been proposed that LTP leads to increased AMPA receptor activity, phosphorylation of Ser-845 by PKA and the recruitment of new receptors to the postsynaptic membrane (Ehlers, 2000; Lee et al., 2000). In contrast, induction of LTD leads to dephosphorylation of the PKA site (Ser-845) via PP2B or PP1 and removal of surface receptors by endocytosis (Ehlers, 2000). More recently, Esteban et al.used a combination of electrophysiological, molecular and pharmacological strategies, to demonstrate that PKA phosphorylation of Ser-845 can regulate the synaptic incorporation of the receptors and LTP (Esteban et al., 2003). They propose that the AMPA receptors are held away from the membrane through an interaction with a retention signal. PKA phosphorylation of the AMPA receptor relieves this signal and allows for insertion into the synapse (Esteban et al., 2003). Furthermore, PKA has been shown phosphorylate the AMPA receptor-interacting protein stargazin (Chen et al., 2000). Stargazin is a membrane-associated protein that binds to the AMPA receptor as well as PSD-95 (postsynaptic density protein of 95 kDa (Chen et al., 2000; Schnell et al., 2002) and allows for the appropriate synaptic localization of the receptors. PKA phosphorylation of stargazin at Thr-321 disrupts the association between stargazin and PSD-95, resulting in a failure of the receptors to cluster at synaptic spines and a down-regulation synaptic AMPA receptor function (Chetkovich et al., 2002; Choi et al., 2002). These data, taken together, suggest that the activity-dependent trafficking of AMPA receptors may be a mechanism to regulate the number of AMPA receptors both rapidly and chronically at the synapse.

Recently, a novel form of PKA-dependent LTD has been identified at the excitatory synapses in the ventral tegmental area (VTA) (Gutlerner et al., 2002). Alterations in synaptic strength at the VTA synapses are thought to be essential in the development of addiction to drugs of abuse (Tong et al., 1995; White, 1996; Wolf, 1998; Mansvelder and McGehee, 2000; Hyman and Malenka, 2001; Gutlerner et al., 2002). The involvement of PKA in LTD in the VTA is interesting because it suggests that PKA "activity" is required for LTD in the VTA whereas, in the hippocampus, it is thought that dephosphorylation of a PKA substrate is important to elicit LTD. Thus, a role for PKA in synaptic plasticity is not just limited to the hippocampus. In addition, auditory fear conditioning in the amygdala is dependant on PKA and protein synthesis (Schafe and LeDoux, 2000).

The persistence of LTP is believed to depend on the transcription and translation of a subset of genes referred to as plasticity-associated genes (Davis and Squire, 1984; Silva and Giese, 1994). The activation of several protein kinase cascades, including PKA, is implicated in the transcription of these genes by regulation of the transcription factor CREB (cAMP responsive element binding protein) (for review see Silva and Giese, 1994 and Silva et al., 1998). A key event in the regulation of CREB is the phosphorylation of its kinase-inducible domain (Gonzalez and Montminy, 1989; Gonzalez et al., 1989; Chrivia et al., 1993). For example, activation of the cAMP-dependent intracellular signaling pathway activates PKA, which in

turn phosphorylates the transcription factor CREB, which then binds to DNA regulatory elements such as CRE (cAMP response element) within the promoter region of target genes and activates transcription (Dash et al., 1990; Karin and Smeal, 1992). It has been shown that the expression of genes containing the CRE element in their promoter is stimulated by synaptic activity that induces LTP (Impey et al., 1998). Moreover, the ability of cAMP analogs to induce LTP is blocked by inhibitors of protein synthesis suggestion that PKA is required for stages of LTP that are dependent on protein synthesis (Frey et al., 1993; Weisskopf et al., 1994). Furthermore, long-term synaptic strength is blocked in experiments in sensory neurons when CREB is titrated out by nuclear injection of oligonucleotides carrying the CRE DNA element (Dash et al., 1990). Studies with CREB mutant mice support a role for CREB in synaptic plasticity and learning and memory. LTP and performance in the Morris water maze task were impaired in some (Bourtchuladze et al., 1994; Kogan et al., 1997; Gass et al., 1998; Falls et al., 2000) but not all CREB mutants (Pittenger et al., 2002).

3. The architecture of AKAPs

Since cAMP and PKA are involved in numerous signaling cascades even within the same cellular compartment, what ensures the specificity of action of each cascade? At least part of the regulation of PKA signaling can be attributed to anchoring proteins that localize kinases and phosphatases to their substrates (Pawson and Scott, 1997). In the case of PKA, A-kinase anchoring proteins (AKAPs) function to compartmentalize PKA to distinct subcellular locations (Colledge and Scott, 1999; Bauman and Scott, 2002; Michel and Scott, 2002).

More than 50 AKAPs have been identified in species ranging from *C. elegans* to humans (Colledge and Scott, 1999; Michel and Scott, 2002). AKAPs have little primary sequence similarity but instead are functionally related. Each AKAP contains a secondary structural motif called an amphipathic helix that binds to the regulatory subunit (R) of PKA with high affinity (Carr et al., 1991; Carr et al., 1992; Newlon et al., 2001). In addition to the conserved R subunit-binding surface, each AKAP contains a unique targeting motif that directs the AKAP complex to a specific subcellular location. AKAPs not only concentrate PKA to allow phosphorylation of specific targets, but also segregate separate cAMP signaling pathways within the same cellular compartment (Colledge and Scott, 1999; Dodge and Scott, 2000; Dodge et al., 2001). Furthermore, AKAPs have been shown to interact with a number of signaling proteins, allowing for the localization and segregation of multi-enzyme signaling complexes (Bauman and Scott, 2002; Michel and Scott, 2002).

4. AKAP79

The capacity of AKAPs to coordinate multienzyme-signaling complexes is exemplified by the neuronal AKAP79 family of anchoring proteins. This family consists of three structurally similar orthologs: AKAP75 (bovine), AKAP150 (mouse), and AKAP79 (human) (Carr et al., 1992). These three proteins are highly related and differ mainly in their molecular weights, a consequence of a repeat sequence present in the N-terminus of AKAP150. These AKAPs are present in the postsynaptic density (PSD) at a majority of mammalian excitatory synapses (Coghlan et al., 1995; Colledge et al., 2000) and are targeted to the plasma membrane by three N-terminal basic regions that bind acidic phospholipids, including phosphatidylinostitol-4,5-bisphosphate (PI-4,5-P2) (Dell'Acqua et al., 1998). Over the past 10 years, extensive effort has been made to identify AKAP79/150 binding partners and to characterize the protein complex. One of the first AKAP79/150 binding partners, PP2B (calcineurin), was identified by a yeast two-hybrid screen using AKAP79 as bait (Coghlan et al., 1995). Since then, several molecular and biochemical studies have confirmed the interaction between the two enzymes (Colledge et al., 2000; Dell'Acqua et al., 2002; Oliveria et al., 2003). Recently, fluorescence resonance energy transfer (FRET) technology has provided further evidence for the assembly of a PKA-AKAP79-PP2B ternary complex in living cells (Dell'Acqua et al., 2002; Oliveria et al., 2003) supporting the biochemical data suggesting that AKAP79 acts as a scaffold for multiple enzymes, some with reciprocal activities. AKAP79/150 also has been shown to associate with and regulate the activity of PKC (Faux and Scott, 1996; Klauck et al., 1996; Faux et al., 1999). Interestingly, the enzymatic activity of PKC is inhibited when bound to the AKAP and the inhibition is relieved upon the binding of calcium/calmodulin, releasing PKC to phosphorylate substrate proteins. AKAP79/150 has been implicated in anchoring PKA, PKC, and PP2B close to several synaptic proteins including NMDA- and AMPA-glutamate receptors (Colledge et al., 2000), the inwardly rectifying potassium channel Kir2.1 (Dart and Leyland, 2001), the β-Adrenergic receptor (Fraser et al., 2000; Cong et al., 2001), mGluR5 metabotropic glutamate receptor (Cho et al., 2002) and GABA receptors at inhibitory synapses (Brandon et al., 2003). Through these interactions, AKAP79/150 can provide a mechanism to direct PKA and other enzymes to the postsynaptic membrane to regulate synaptic activity.

4.1. AKAP79/150 and LTP and LTD

A role for AKAP-anchored PKA in modulating synaptic activity was first demonstrated by Rosenmund et al.who showed that peptide-mediated disruption of the AKAP-PKA association attenuates AMPA receptor currents and synaptic events (Rosenmund et al., 1994). Since then, efforts have been put forth to understand the molecular mechanisms governing this regulation. It is now clear that regulation of PKA phosphorylation of AMPA receptors plays a role in establishment of LTP and LTD. The identification of an interaction between AKAP79/150 and the membrane associated guanylate kinase (MAGUK) synaptic scaffolding proteins, SAP97 and PSD-95, linked AKAP79/150 to synaptic AMPA receptors and provided a mechanism by which AKAP79/150 may regulate postsynaptic excitatory transmission (Colledge et al., 2000). The N-terminal PDZ domains of PSD-95 and SAP97 associate with the C-terminal tails of NMDA and AMPA glutamate receptors, respectively. The C-terminal SH3 and GK regions of the MAGUKs bind to AKAP79/150 (Colledge et al., 2000). In this way, through simultaneous association with the MAGUKs, glutamate receptors and PKA are recruited into a macromolecular signaling complex at excitatory synapses.

Recently, attention has focused on the regulation of AMPA receptor phosphorylation and localization by PKA and PP2B pathways coordinated by the AKAP79/150-MAGUK protein complex. A series of molecular, biochemical and electrophysiological experiments established that AKAP79/150-anchored PKA phosphorylates Ser-845 on GluR1 resulting in alteration of channel activity (Colledge et al., 2000; Tavalin et al., 2002) and that the PKA site is selectively dephosphorylated during LTD (Kameyama et al., 1998; Lee et al., 2000). It has been suggested that AKAP79/150-associated PP2B may be the predominant phosphatase opposing the action of PKA on hippocampal AMPA receptors (Banke et al., 2000; Dell'Acqua et al., 2002; Tavalin et al., 2002). This implies that the balance between anchored kinases and phosphatases is an important determinant in the regulation of AMPA receptor activity and may govern changes in synaptic plasticity (Fig. 1).

AKAP-directed kinase/phosphatase complexes have been implicated in the regulation of AMPA receptor surface expression, a process thought to contribute to LTP and LTD. As mentioned earlier, several studies indicate that changes in the synaptic levels of AMPA receptors represent a mechanism for the rapid modulation of synaptic efficacy (Ehlers, 2000; Lee et al., 2000; Liu and Cull-Candy, 2000; Luscher et al., 2000; Malinow et al., 2000; Esteban et al., 2003). Moreover,

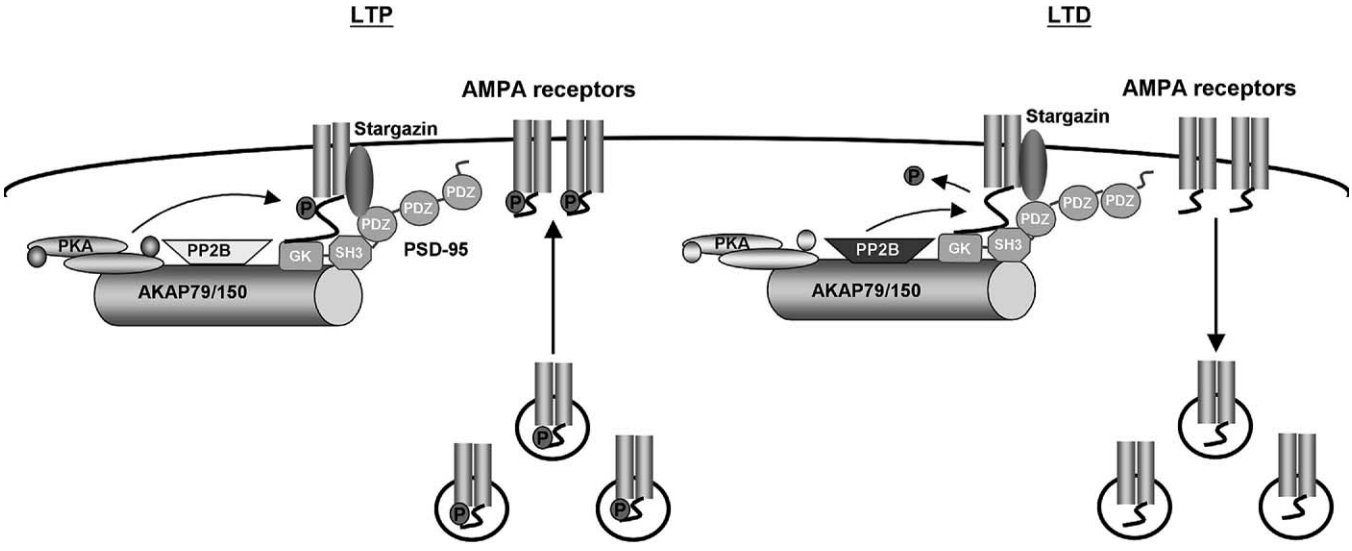

Fig. 1. Regulation of glutamate receptor trafficking by the AKAP79/150 protein complex during LTP or LTD. The association of AKAP79/150 with PSD-95 brings anchored PKA and PP2B in close proximity to AMPA receptors in the postsynaptic membrane. (Left) LTP results in an increase in the number of AMPA receptors at the membrane as well as an increase in channel activity. High frequency stimulation of the neuron results in the activation of the AKAP anchored PKA and subsequent phosphorylation of the C-terminal tail of AMPA receptors at the membrane. Phosphorylation potentates receptor function by increasing the peak open probability. Furthermore, activated PKA phosphorylated the C-terminal tail of vesicle-associated AMPA receptors inside the cell. Phosphorylation of these receptors relieves a retention signal and allows for the receptors to be inserted into the plasma membrane. (Right) LTD results in a decrease in the number of AMPA receptors at the postsynaptic density. The phosphatase PP2Bis activated by the increase in intracellular calcium resulting from the activation of NMDA receptors by low frequency stimulation. The active phosphatase dephosphorylates the PKA site in the C-terminal tail of the membrane associated AMPA receptors. The dephosphorylation results in the endocytosis and removal of the receptors from the membrane.

PKA phosphorylation of AMPA receptors or AMPA receptor interacting proteins, such as stargazin, may also play a role in these regulated trafficking events (Chetkovich et al., 2002; Schnell et al., 2002; Esteban et al., 2003; Lee et al., 2003). In addition, as mentioned above, stargazin, interacts PSD-95 (Schnell et al., 2002) establishing another link through which AKAP-anchored PKA may be directed to AMPA receptors. Interestingly, uncoupling stargazin from the AMPA receptor or PSD-95, events that would subsequently result in the uncoupling of the AKAP signaling complex from the receptor, leads to a decrease in the surface expression of AMPA receptors (Schnell et al., 2002). Recently, Gomez et al.have shown that NMDA-PP2B signaling pathways controlling AMPA receptor trafficking also negatively regulate the localization and association of the endogenous AKAP/150-PKA complex with PSD-95 in neurons (Gomez et al., 2002). These findings suggest that AKAP anchored PKA and PP2B can play a major role in regulating AMPA receptor surface expression and in turn synaptic plasticity.

5. WAVE1

Another AKAP known to assemble and coordinate multi-protein complexes in neurons is WAVE1. WAVE1 belongs to the Wiskott-Aldrich syndrome protein (WASP) family, which includes the WASPs (WASP and N-WASP) and the three SCAR/WAVEs members (WAVE1, WAVE2, and WAVE3). These proteins are cytoplasmic molecules that link Rho GTPases to actin assembly (Machesky and Insall, 1998; Suetsugu et al., 1999; Takenawa and Miki, 2001). The WAVEs share a conserved Verprolin-Cofilin-Acidic (VCA)-rich domain that mediates binding to and activation of Arp2/3. (Machesky and Insall, 1998; Miki et al., 1998; Suetsugu et al., 1999). In addition, the WAVEs contain a SCAR homology domain (SHD) (Suetsugu et al., 1999). In response to activation of small Rho GTPases, WASPs stimulate the nucleating activity of the Arp2/3 complex, resulting in the formation of specific cell surface projections known as lamellipodia and filopodia (Miki et al., 1998; Takenawa and Miki, 2001). Recently, in growth cones of neurons, WAVE1 was shown to localize to the leading edge of lamellipodia (a sheet-like cell structure formed by polymerizing actin) (Hahne et al., 2001; Nozumi et al., 2003), but not filopodia (a thin extension also formed by polymerizing actin) (Nakagawa et al., 2003; Nozumi et al., 2003). The SHD of WAVE1 is thought to determine its localization in the lammellipodia (Hahne et al., 2001; Nozumi et al., 2003).

Several pieces of evidence suggest WAVE1 plays a role in actin polymerization and recent identification of WAVE1 interacting proteins has shed light on how WAVE1 might regulate this process (Fig. 2). The rate-limiting step in actin polymerization is the assembly of actin monomers into a trimer (Higgs, 2001). WAVE1 may enhance polymerization by acting as a scaffold bringing Arp2 close to Arp3 for nucleation with a pre-existing actin filament, presumably mimicking an actin trimer (Machesky and Insall, 1998; Machesky et al., 1999; Robinson et al., 2001). Recent work proposes that Rac and the adapter protein Nck may activate actin polymerization through WAVE1 (Eden et al., 2002). WAVE1 is suggested to exist in a complex that includes the p53-inducible PIR121, the Nck-associated protein NAP125, the Abl Interactor protein Abi2, and a small actin-stimulating peptide, HSPC300 (Eden et al., 2002). This complex is believed to be inactive because WAVE1 is unable to bind the Arp2/3 complex (Takenawa and Miki, 2001; Eden et al., 2002), although other models exist (Prehoda et al., 2000). To relieve this inhibition, GTP-bound Rac or the recruitment of Nck activates the WAVE complex by an unknown mechanism. One model suggests activated Rac or Nck may bind PIR121, NAP125 and Abi2 thus releasing an active WAVE1/HSPC300 complex (Eden et al., 2002). WAVE1/HSPC300 can then interact with the Arp2/3 complex to promote actin nucleation (Eden et al., 2002). Rac signaling to actin is then proposed to be attenuated by recruitment of the Rac-selective GTPase activating protein WRP by WAVE1, which hydrolyzes Rac to the inactive GDP bound form (Soderling et al., 2002) and terminates actin polymerization.

WAVE1 also has been shown to interact with a number of other proteins including the RII subunit of PKA and Abelson tyrosine kinase (Abl) (Westphal et al., 2000). Intriguingly, the RII-binding region of WAVE1 overlaps with the actin-binding domain, and in vitro competition experiments show that actin competes for the RII-binding site. This result suggests that competition between the RII subunit of PKA and actin may regulate the function of WAVE1 (Westphal et al., 2000). Based on these results, WAVE1 is proposed to function as a scaffolding protein to organize protein networks of actin-binding proteins, adapter proteins, signaling enzymes and the Arp2/3 complex (Scott, 2003).

Actin polymerization is believed to play a role in synaptic plasticity and learning and memory. Evidence suggests that remodeling of synapses occurs after hippocampus-dependent learning (Geinisman, 2000; Geinisman et al., 2000). These morphological changes also occur within synapses upon induction of LTP and may depend on actin reorganization (Fischer et al., 1998; Engert and Bonhoeffer, 1999; Matus, 2000; Fukazawa et al., 2003). In support of this notion, inhibition of actin polymerization impairs L-LTP (Fukazawa et al., 2003). Since WAVE1 functions in actin cytoskeletion reorganization and it localizes to the

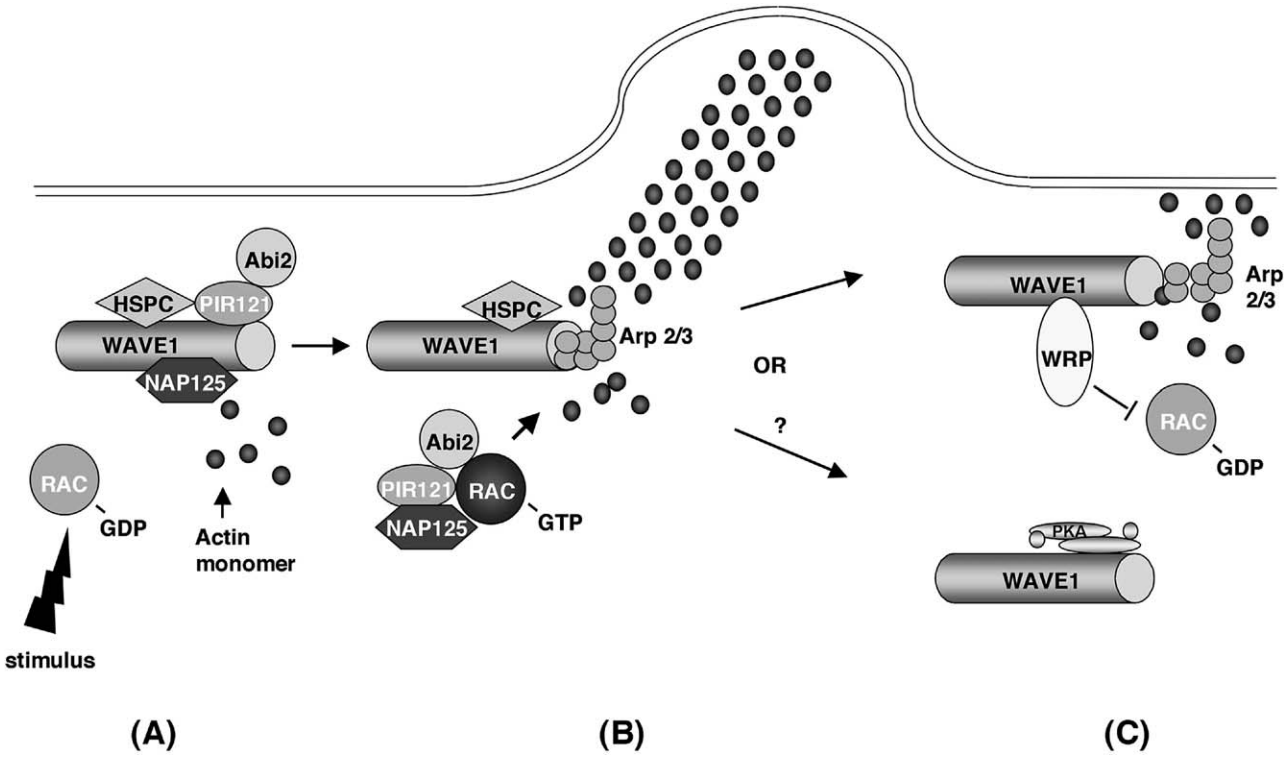

Fig. 2. Role of WAVE1 signaling complex in lamellipodia formation. (A) In the absence of a stimulus, WAVE1 is held inactive in a complex with Nap125, HSPC300, PIR121 and Abi2 proteins. (B) Once a stimulus activates Rac, GTP bound Rac binds to Nap125, PIR121 and Abi2, thus releasing WAVE1 and HSPC300. Although Rac stimulates actin polymerization, it is not clear if the Nap125, PIR121, Abi2 complex also participates in this function. The WAVE1/HSPC300 complex binds to the Arp2/3 complex and stimulates actin bundle formation, which results in the formation of the sheet-like cell formation known as lamellipodia. (C) Upper, the termination of Rac stimulation of actin polymerization occurs when WRP hydrolyzes Rac to the inactive GDP bound form. Lower, alternative evidence suggests PKA competes for the actin-binding site, which could displace actin and terminate actin polymerization.

leading edge of lamellipodium, WAVE1 is implicated in neurite outgrowth by regulating actin remodeling events (Nozumi et al., 2003). The localization of WAVE1 and its role in actin polarization also suggests that WAVE1 may also function in synaptic plasticity.

Insight into the role of WAVE1 in neuronal function comes from the characterization of WAVE1 knockout mice. Inactivation of WAVE1 in mice indicates that at least some of the WAVE1 binding proteins and WAVE1 play a role in a variety of normal behaviors (Soderling et al., 2003). WAVE1 knockout mice displayed defects in the Morris water maze task, suggesting defects in hippocampal learning and memory. Furthermore, WAVE1 knockout mice displayed defects in two tests (novel open arena and elevated zero-maze) used to determine anxiety levels associated with neural networks in the amygdala. Finally, WAVE1 knockout mice also displayed poor performance in three tests for balance and coordination (rotarod, inclined screen and balance beam tests). Additional analysis is necessary to determine if WAVE1 anchoring of PKA and the other enzymes is responsible for some or all of the defects in memory that are apparent in the WAVE1 knockout mice. Intriguingly, mutations in WRP (MEGAP/srGAP3), a gene disrupted in patents suffering from 3p-syndrome mental retardation, also results impaired learning and memory, poor balance, and reduced coordination (Endris et al., 2002). Moreover, several Rho Family GTPases have been linked to mental retardation, and the regulation of the actin cytoskeleton is suggested to be causally involved in mental retardation (Ramakers, 2002). Thus, WAVE1 localization of WRP could be important for learning and memory, regulation of the actin cytoskeleton and possibly neurite outgrowth (Soderling et al., 2003). Subsequently, another group has inactivated WAVE1 in mice using a retroviral gene trap to generate the knockout (Dahl et al., 2003). Although both groups did notice that the disruption of WAVE1 resulted in runted stature and postnatal lethality, Dahl et al. found that the knockout of WAVE1 leads to postnatal lethality (Dahl et al., 2003) while Soderling et al.reported only 30% postnatal lethality (Soderling et al., 2003). The reason for these differences in the WAVE1 knockout mice are still unknown, but could be related to a strain background difference.

6. Conclusions

The studies summarized in this review indicate that PKA and its AKAPS may be key contributors to the synaptic changes that encode memories. Biochemical, molecular and genetic experiments suggest that the appropriate localization and targeting of PKA via AKAPs is important for regulating PKA activity during synaptic plasticity. AKAP79/150 preferentially targets kinases, such as PKA and PKC, and phosphatases, such as PP2B, to glutamate receptors at the postsynaptic density (Colledge et al., 2000). The balance that exists between AKAP79/150-anchored kinase and phosphatase activity alters glutamate receptor function and may underlie changes in synaptic plasticity (Colledge et al., 2000; Tavalin et al., 2002). Although a role for WAVE1 in LTD or LTP has not been identified, several pieces of evidence suggest that WAVE1 may affect processes involved in learning and memory. WAVE1 is localized to lamellipodia and is involved in actin polymerization at the leading edge of growth cones (Hahne et al., 2001; Nozumi et al., 2003). The WAVE-dependent actin polymerization may be important for neurite outgrowth, a process that governs the formation of appropriate synaptic connections during development as well as changes in dendritic structure during learning (Engert and Bonhoeffer, 1999; Matus, 2000; Colicos et al., 2001; Trachtenberg et al., 2002). In addition, loss of WAVE1 suggest it is required for normal neural functioning (Soderling et al., 2003). Future efforts should be directed at characterizing and developing knockout mice to dissect the pathways involved in the learning and memory.

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