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Regulation of hippocampus-dependent memory by cyclic AMP-dependent protein kinase

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Abstract

The hippocampus is crucial for the consolidation of new declarative long-term memories. Genetic and behavioral experimentation have revealed that several protein kinases are critical for the formation of hippocampus-dependent long-term memories. Cyclic-AMP dependent protein kinase (PKA) is a serine–threonine kinase that has been strongly implicated in the expression of specific forms of hippocampus-dependent memory. We review evidence that PKA is required for hippocampus-dependent memory in mammals, and we highlight some of the proteins that have been implicated as targets of PKA. Future directions and open questions regarding the role of PKA in memory storage are also described.

Keywords

memory; learning; cyclic AMP-dependent protein kinase; hippocampus; synaptic plasticity; long-term potentiation

Introduction

Protein kinases modulate a plethora of important processes, including synaptic plasticity, learning, and memory. Multiple chemical neurotransmitters, hormones, and other signaling substances use cyclic adenosine 3',5'-monophosphate (cAMP) as an intracellular second messenger. The principal target for cAMP in mammalian cells is cAMP-dependent protein kinase (PKA), which is ubiquitously expressed and mediates intracellular signal transduction. Pioneering work by Earl Sutherland identified cAMP as the first intracellular second messenger (Sutherland and Rall, 1957; Sutherland et al., 1965). Subsequently, Edwin Krebs, Paul Greengard, and their colleagues purified PKA from rabbit skeletal muscle (Walsh et al., 1968; Reimann et al., 1971), and they showed that PKA activity was stimulated by cAMP (Miyamoto et al., 1968, 1969; Walsh et al., 1968; Beavo et al., 1974). Other advances, made possible by genetic, molecular, and cell biological techniques, have shed light on the molecular characteristics, dynamics, and functional plurality of the PKA holoenzyme (reviewed by McKnight et al., 1988; Beebe, 1994; Skalhegg and Tasken, 2000). It is now well established that PKA regulates many biological processes through its phosphorylation of proteins. Also, phosphatases such as protein phosphatase 1 and the calcium-regulated phosphatase, calcineurin, can dephosphorylate proteins that had been phosphorylated by PKA, thus allowing PKA signaling events to be reversible (Fig. 1).

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A fundamental process that is modulated by PKA is synaptic transmission, which can be modified by the electrical activity of a neuron—a process termed “activity-dependent synaptic plasticity” (reviewed by Nguyen and Woo, 2003). Because synaptic plasticity involves long-lasting modifications of intercellular signaling in the nervous system, it plays significant roles in regulating learning and memory (Castellucci et al., 1970; Kupfermann et al., 1970; McKernan and Shinnick-Gallagher, 1997; Abraham et al., 2002; Whitlock et al., 2006). Not surprisingly, certain types of long-lasting synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD), are believed to underlie some forms of learning and memory in the mammalian brain (Bliss and Lomo, 1973; Dudek and Bear, 1992; Martin et al., 2000; Abraham et al., 2002; Whitlock et al., 2006).

Cyclic AMP/PKA signaling has been shown to be pivotal for specific types of long-term synaptic plasticity and for long-term memory (Fig. 1), as demonstrated in the landmark studies of learning and memory in *Aplysia* and *Drosophila* (reviewed by Burrell and Sahley, 2001). In particular, electrophysiological and behavioral studies of the marine snail, *Aplysia californica*, have revealed a requirement for cAMP/PKA signaling in the establishment of short- and long-lasting forms of synaptic plasticity, learning, and memory (Kandel, 2001). These studies demonstrated an important role for PKA in mediating short-term synaptic facilitation (by reversible phosphorylation of ion channels), and long-term facilitation and long-term memory for behavioral sensitization (by modulation of gene expression and protein synthesis) (Kandel, 2001). Studies in *Drosophila* have also been instrumental in defining the role of PKA in learning and memory (reviewed by McGuire et al., 2005; Davis, 1996). The learning mutant, *dunce*, was the first learning mutant isolated in *Drosophila*, and *dunce* encodes a cAMP phosphodiesterase. Similarly, mutations in adenylyl cyclase (*rutabaga*) and mutations in PKA itself impair learning and memory in *Drosophila*. Overall, these landmark experiments have laid much of the conceptual foundations for subsequent research on the roles of PKA in learning and memory in the mammalian brain. In this article, the roles of PKA in hippocampus-dependent memory are reviewed. We focus only on the mammalian hippocampus, because of its pivotal roles in the consolidation of spatial and non-spatial long-term memories. We discuss studies that have shown a requirement for PKA signaling in the hippocampus. We then consider some of the downstream targets of PKA, emphasizing studies that have identified requirements for PKA-mediated phosphorylation and signaling in hippocampal LTP, a form of synaptic plasticity that has been linked to memory formation (Abel et al., 1997; Gruart et al., 2006; Whitlock et al., 2006).

cAMP-dependent protein kinase (PKA)

The mammalian PKA family consists of four regulatory (R) subunits (RI α , RI β , RII α , RII β) and three catalytic (C) subunits (C α , C β , C γ). Each subunit is encoded by a unique gene (McKnight et al., 1988; Doskeland et al., 1993) and they are all expressed in the mammalian brain (Cadd and McKnight, 1989). Two major isozymes of PKA, termed type I (with RI α and RI β dimers) and type II (with RII α and RII β dimers), have been characterized and were initially identified based on their patterns of chromatographic elution (Tasken et al., 1993; Francis and Corbin, 1999; Skalhegg and Tasken, 2000). In the absence of cAMP, PKA is an inactive tetrameric holoenzyme composed of two R subunits bound to two C subunits. Each regulatory subunit contains two tandem cAMP binding sites, a high-affinity site and a low-affinity site (Taylor et al., 1990). Sequential and cooperative binding of cAMP to these two sites releases monomeric C subunits (Taylor et al., 1990; Gibbs et al., 1992). These dissociated C subunits can then phosphorylate serine and threonine residues on numerous proteins. In essence, the regulatory subunits inhibit the phosphotransferase activities of the catalytic subunits.

Properties of memory

Learning, the change in behavior as a result of experience, and memory, the retention of changes in behavior that result from learning, have been of great interest to neurobiologists. The psychological study of memory began over 100 years ago with the experiments of Herman Ebbinghaus; since then, researchers have sought to define the principles underlying memory storage. This work has defined three major properties of memory storage (Milner et al., 1998). First, the study of patients like H. M. revealed that there are multiple memory systems that function in distinct but overlapping ways. Thus, declarative or explicit memory, the conscious memory of facts and events, is mediated by the hippocampal memory system, whereas non-declarative or implicit memory, involving unconscious learning of emotional tasks or skills and habits, is mediated by other brain systems such as the amygdala and striatum. Secondly, memory consists of specific temporal phases, including short-term and long-term memory. As we will see in our discussion here of the cAMP/PKA signaling pathway, these phases of memory can be mediated by distinct molecular pathways. Thirdly, memory consists of specific stages. Memory is acquired during training, consolidated in the period following training into a more stable form, and then retrieved when needed. Following retrieval, memory can be modified by processes of reconsolidation and extinction. In this review, we will focus on the role of the cAMP/PKA signaling pathway in hippocampus-dependent forms of memory in rodents.

The role of the cAMP/PKA system in spatial memory

In rodents, the quintessential hippocampus-dependent behavioral task is spatial learning and memory in the hidden platform version of the Morris water maze. In this task, animals learn to use the distal cues located in the room to find the location of a submerged platform during repeated trials. Performance is measured by an increase in latency to find the platform during training trials and memory is tested in a probe (or transfer) test in which the platform is removed from the pool and animals swim freely. During this probe test, the spatial preference of the animals is measured by a tracking device and spatial learning is reflected in a spatial bias to this search pattern: well-trained animals spend most of their time swimming in the vicinity of the platform location. This form of spatial learning depends on the dorsal hippocampus and it is NMDA receptor-dependent (Morris et al., 1982, 1986; Tsien et al., 1996). Importantly, the water maze can be configured in many different ways: with a visible platform that is shifted from trial to trial to test for procedural memory, or with a hidden platform that is shifted from day to day to test for working memory. As typically configured with a positionally fixed hidden platform, the water maze tests spatial reference memory. In addition to the water maze, spatial memory can also be tested in the radial arm maze and in the Y maze.

What is the role of the cAMP/PKA signaling pathway in spatial memory? This issue has been difficult to address genetically because of redundancy in the genes encoding various components of the cAMP/PKA signaling pathway, particularly PKA itself. In addition, the large number of training trials in the water maze makes region-specific pharmacological manipulation difficult. Initial work in the mammalian hippocampus defined a role for cAMP and PKA in synaptic plasticity (reviewed in Nguyen and Woo, 2003). The first demonstration of a role for cAMP in spatial memory came in 1995 when Daniel Storm and colleagues examined the effects of mutations in the gene encoding type I adenylyl cyclase on behavior (Wu et al., 1995). They found that mutant mice lacking type I adenylyl cyclase had reductions in the levels of calcium-stimulated cAMP synthesis and exhibited spatial memory deficits in the hidden platform version of the water maze (Wu et al., 1995). Studies of similar conventional null mutations in the genes encoding specific regulatory and catalytic subunits of PKA were difficult to interpret because of compensatory changes in the

expression of genes encoding other PKA subunits in these mutant mice (Brandon et al., 1997). Also, the behavioral phenotypes observed in mutant mice is sensitive to genetic background (Howe et al., 2002). To define the role of PKA in learning and memory in rodents, Abel et al. (1997) created R(AB) transgenic mice expressing a dominant negative form of the regulatory subunit of PKA. By using a transgenic approach, PKA can be inhibited in specific cell types at particular times, thereby reducing potential compensatory effects. Furthermore, the R(AB) transgene will interfere broadly with type I PKA within the cell types in which it is expressed. In the initial R(AB) transgenics, the CaMKII α promoter restricted expression to postnatal excitatory neurons within the forebrain. These transgenic mice have provided the clearest demonstration that PKA activity is critical for spatial memory, as these mice exhibited normal initial learning in the hidden platform version of the water maze, but showed deficits in memory in retrieval tests. Biochemical studies of PKA activation following training have revealed that spatial learning activates PKA in the hippocampus. Interestingly, such activation is observed early in learning at a time when PKA inhibition does not impair performance, suggesting that PKA activation during training sets into motion a biochemical cascade that leads to memory storage (Vazquez et al., 2000; Mizuno et al., 2002). Such a cascade may likely involve the activation of ERK (extracellular signal-regulated protein kinases) and the transcription factor, CREB (cAMP response element binding protein).

Few studies have probed the effects of pharmacological inhibitors of PKA on spatial learning, perhaps because of the assumption that PKA would need to be inhibited during each training trial. Surprisingly, a single infusion of H-89, an inhibitor of PKA, into area CA1 of the dorsal hippocampus after the last trial on the third day of training significantly impaired spatial memory (Sharifzadeh et al., 2005). Clearly, additional pharmacological studies are needed to define the role that PKA might play earlier in acquisition or during retrieval, reconsolidation, and extinction of spatial memory. As always with pharmacological studies, it is important to note that the effects of inhibitors are rarely specific (Davies et al., 2000).

The role of the cAMP/PKA system in contextual conditioning

Experiments with spatial memory clearly establish the role of the cAMP/PKA pathway in hippocampus-dependent memory. However, because of the repeated training trials necessary for spatial learning, these tasks do not allow researchers to precisely define the role of this signaling pathway in short- and long-term memory. Since 1890, when William James made the distinction between short-term and long-term memory (James, 1890), researchers have sought to determine the relationship between these processes. Using single-trial learning tasks such as contextual fear conditioning and step-down inhibitory avoidance, researchers can define the mechanisms underlying short-term and long-term memory in the mammalian brain. In contextual fear conditioning, animals are exposed to a novel context and receive a mild footshock. A single 2- to 3-min training trial is sufficient for rodents to exhibit fear when re-exposed to the conditioning context. Such a fear response is measured most frequently by immobility (“freezing”). Contextual fear conditioning is sensitive to lesions of the amygdala and hippocampus (reviewed by Maren, 2001). Importantly, cued fear conditioning, in which animals are exposed to a tone and a footshock, is sensitive to lesions of the amygdala but not to hippocampal lesions, providing a good behavioral control for experiments aimed at addressing the impact of manipulations on hippocampal function.

The first evidence that PKA played a role in contextual fear conditioning came from studies of R(AB) transgenic mice (Abel et al., 1997; Bourchouladze et al., 1998). These mutant mice exhibited selective deficits in long-term memory for contextual fear conditioning. Short-term memory for contextual fear as well as cued fear conditioning were intact. More

recent R(AB) transgenic lines have used the tetracycline system for conditional regulation in adulthood, and these studies have confirmed that genetic inhibition of neuronal PKA in adulthood selectively impairs contextual long-term memory (Isiegas et al., 2006). Mice lacking the calcium-responsive forms of adenylyl cyclase also exhibit selective long-term memory deficits in contextual conditioning and passive avoidance, but the time course of these deficits appears to be distinct from that observed in the PKA mutant mice, perhaps because of differences in experimental procedures or genetic backgrounds of the different mutant mice (Wong et al., 1999). Although most research has focused on aversive conditioning, recent studies using novel object recognition have also revealed an important role for cAMP signaling in long-term memory in this non-aversive task (Pineda et al., 2004; Wang et al., 2004). Interestingly, studies in invertebrates (*Drosophila*, *Aplysia*) have found that the cAMP/PKA pathway is involved in short-term and long-term memory. In contrast, the majority of the studies in vertebrate systems have found that the cAMP/PKA signaling pathway plays a selective role in long-term memory. The reasons for this distinction are unclear.

Intra-ventricular or intra-hippocampal injection of PKA inhibitors has been shown to impair long-term contextual memory (Bourtchouladze et al., 1998; Wallenstein et al., 2002; Ahi et al., 2004). In experiments using step-down inhibitory avoidance, Izquierdo and colleagues have also found that inhibitors of PKA administered into hippocampal area CA1 selectively impair long-term memory (Bernabeu et al., 1997; Vianna et al., 2000; Quevedo et al., 2004). In rodents, inhibitors of protein synthesis impair long-term memory, similar to inhibitors of PKA, suggesting that PKA plays a role in activating the biochemical mechanisms that engage protein synthesis and transcription.

Much research has focused on the idea that PKA targets transcriptional machinery (Fig. 1). One target of PKA of great interest has been CREB, and CREB phosphorylation is increased after fear conditioning, as is expression of a CRE-driven reporter gene (Impey et al., 1998; Stanciu et al., 2001; Athos et al., 2002; Mizuno et al., 2002). It is important to note in this context that PKA is one of several kinases that can phosphorylate CREB on serine 133, and identifying which kinase is most critical under specific behavioral circumstances remains a challenge (Athos et al., 2002; Sindreu et al., 2007). The analysis of CREB mutant mice, however, has not been as clearly in support of a selective role for CREB in long-term memory as one might have expected, perhaps because of compensatory changes in other CRE-binding proteins in CREB mutant mice (Hummler et al., 1994) or because of effects of genetic background (Bourtchouladze et al., 1994; Gass et al., 1998; Bucan and Abel, 2002; Graves et al., 2002; Balschun et al., 2003). Indeed, the data appear to be more consistent with the idea that a CRE-binding protein related to CREB is involved in long-term memory storage, because the clearest phenotypes have been observed in genetically modified mice expressing dominant-negative forms of CREB (Kida et al., 2002; Pittenger et al., 2002), which effectively interfere with many proteins binding to CRE sites, and in CBP mutant mice, which also interfere with the action of a number of transcription factors (Oike et al., 1999; Bourtchouladze et al., 2003; Alarcon et al., 2004; Korzus et al., 2004; Wood et al., 2005, 2006).

The study of the molecular mechanisms underlying memory storage has highlighted important questions about the nature of memory. First, what is the relationship between long-term and short-term memory? Is short-term memory a process on the way towards long-term memory or are these two forms of memory mediated by independent, parallel processes? Most treatments that impair short-term memory also impair long-term memory, suggesting that in many cases they are serial processes. However, under certain circumstances, treatments can lead to impairments in short-term memory without impairing long-term memory, implying that these forms of memory can be mediated by distinct,

parallel mechanisms (Emptage and Carew, 1993; Izquierdo et al., 1998; Sherff and Carew, 2004). Secondly, is memory consolidation a single process set into motion by training or does it have distinct phases? Here the data from studies of the role of PKA in long-term memory storage suggest that there are at least two time periods during which PKA and protein synthesis are required during memory consolidation (Bernabeu et al., 1997; Bourtchouladze et al., 1998). Finally, what is the behavioral role of cAMP/PKA signaling in the hippocampus and how does this compare to the role of this signaling pathway in other brain regions?

It is interesting to note that genetically modified mice in which the PKA pathway has been manipulated exhibited selective deficits in contextual fear conditioning, with intact cued fear conditioning (Abel et al., 1997; Isiegas et al., 2006). This suggests that the cAMP/PKA signaling pathway has distinct roles in the hippocampus and the amygdala, because direct pharmacological manipulation of PKA in the amygdala impairs cued fear conditioning (Schafe and LeDoux, 2000). In addition, it may be that the hippocampus forms a representation of the context during training whereas the amygdala may be the site of the association of the conditioned and unconditioned stimuli (CS and US) (Maren, 2001; Keeley et al., 2006). If this is the case, then there may be fundamental biochemical differences in the ways in which circuits in the hippocampus and amygdala are activated by training. Future experiments will be required to investigate these issues.

The cAMP/PKA pathway as a target of cognition-enhancing drugs

Our discussion has focused on the impact of impairments in cAMP/PKA signaling, but researchers have also investigated the behavioral effects of increased activity in the cAMP/PKA pathway. Pharmacological experiments have revealed a time window of 3–6 h after training when treatment with drugs that directly or indirectly activate PKA can enhance memory storage (Bernabeu et al., 1997). Blockade of the degradation of cAMP by treatment with inhibitors of phosphodiesterases such as the PDE4 inhibitor, rolipram, enhances memory (Barad et al., 1998). Interestingly, these PDE inhibitors can reverse the memory impairments found in aged mice (Bach et al., 1999) and in mouse models of mental retardation (Bourtchouladze et al., 2003) and Alzheimer's Disease (Vitolo et al., 2002; Gong et al., 2004). Although the benefits of pharmacological blockade of PDE for memory storage have been known for some time, the use of this approach in human patients is still in its nascent stages (Rose et al., 2005).

Studies of genetic manipulations designed to increase levels of cAMP have revealed that it is important to distinguish between manipulations that increase cAMP *levels* and those that increase cAMP *signals*. Genetic manipulations that increase cAMP *signals* (such as overexpression of calcium-responsive adenylyl cyclase) lead to memory enhancements like those observed with PDE inhibitors, whereas genetic manipulations that increase basal cAMP *levels* lead to memory impairments (Pineda et al., 2004; Wang et al., 2004; Bourtchouladze et al., 2006).

Synaptic tagging

Neurons typically receive inputs from thousands of synaptic contacts. However, L-LTP is input-specific (Andersen et al., 1977; Nguyen et al., 1994). To preserve the input specificity of L-LTP, a mechanism to mark, or “tag”, active synapses has been proposed to allow newly synthesized gene products to be captured and utilized at appropriately activated synapses (Sossin, 1996; Frey and Morris, 1997; Schuman, 1997). Frey and Morris (1997) first provided evidence for the synaptic tag theory in the rat hippocampus. They proposed that proteins synthesized in response to long-term synaptic changes at one set of synapses could be captured and utilized by other synapses to express L-LTP if a synaptic tag is generated by

appropriate synaptic activity. In accordance with this idea, they found that transient potentiation resulting from weaker synaptic activation could be prolonged to resemble L-LTP if paired with established protein synthesis-dependent L-LTP at separate synaptic inputs (Frey and Morris, 1997).

Interestingly, low-frequency stimulation (LFS) can impair L-LTP subsequently induced at the previously activated synapses (homosynaptic inhibition), as well as at other synapses converging on the same postsynaptic cells (heterosynaptic inhibition) (Young and Nguyen, 2005). Both homosynaptic and heterosynaptic inhibition of L-LTP by prior LFS required protein phosphatase activity (Young et al., 2006), and LFS impaired signaling through the cAMP/PKA pathway (Young et al., 2006). More importantly, pharmacological or genetic inhibition of PKA impaired synaptic capture, and pharmacological activation of cAMP/PKA signaling was sufficient to generate a synaptic tag that enabled persistent synaptic facilitation (Young et al., 2006). Thus, PKA has a key role in synaptic tagging that may be a novel control point in the consolidation of L-LTP, and perhaps, of long-term memory. PKA-mediated signaling can be constrained by prior episodes of synaptic activity to regulate future L-LTP expression and the spatiotemporal integration of multiple synaptic events. Because there is evidence that a behavioral analog of synaptic tagging and capture may occur during spatial exploration of a novel environment (Moncada and Viola, 2007), it will be of interest to determine, by *in vivo* inhibition of PKA, whether PKA also has a role in producing this modification of behavioral learning and memory.

Downstream substrates for PKA in synaptic plasticity and memory storage

The cAMP/PKA signaling cascade has garnered much attention because of its critical requirement for both long-term memory and for specific forms of long-term synaptic plasticity that are believed to underlie memory storage. The precise molecular mechanisms underlying these processes have not been fully elucidated, but many proteins that are important mediators of synaptic plasticity are regulated by cAMP/PKA signaling (Fig. 1; reviewed by Nguyen and Woo, 2003). Here, we discuss several key proteins that are targets of PKA and that have been implicated in mediating the induction and expression of hippocampal LTP, an activity-dependent enhancement of synaptic strength that is believed to be a cellular mechanism for information storage in the mammalian brain (Bliss and Collingridge, 1993; Martin et al., 2000; Gruart et al., 2006; Whitlock et al., 2006). These proteins include NMDA (*N*-methyl-D-aspartate) and AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate) glutamatergic receptors, RIM1 α , inhibitor-1 (I-1, an inhibitor of protein phosphatase-1), and the transcription factor, CREB (Fig. 1). We highlight these substrates to underscore the notion that PKA signaling is important for the expression of hippocampus-dependent forms of memory because it can modify specific signal transduction molecules that are critical for hippocampal LTP, a type of synaptic plasticity that has been strongly correlated with memory storage.

NMDA receptors (NMDARs)

In rat (Collingridge et al., 1983) and mouse (Tsien et al., 1996; Woo et al., 2003) hippocampal area CA1, LTP induction requires activation of NMDARs. Pharmacological block of brain NMDARs impairs spatial learning and attenuates hippocampal LTP in rats (Morris et al., 1986). Genetic knockout of NMDARs in area CA1 *per se* impairs spatial learning in the Morris water maze and blocks induction of LTP (Tsien et al., 1996). At the molecular level, PKA is coupled directly to NMDARs through an A-kinase anchoring protein (AKAP), yotiao, which permits modulation of NMDAR channel activity by PKA (Westphal et al., 1999). Recent studies by Suzanne Zukin and her colleagues have shown that pharmacological blockers of PKA reduce both the calcium permeability of NMDARs and NMDAR-mediated calcium signals in active dendritic spines of rodent hippocampal

neurons (Skeberdis et al., 2006). The same blockers of PKA attenuated LTP at Schaeffer collateral-CA1 synapses (Skeberdis et al., 2006), thus linking PKA-dependent synaptic plasticity to calcium signaling in spines and to calcium permeability of NMDARs. Interestingly, this regulation of NMDAR currents by PKA was more prominent in neurons cultured from immature animals, suggesting developmental regulation of PKA modulation of these currents (Skeberdis et al., 2006). Thus, PKA phosphorylates the NMDAR or another associated protein, thereby altering the size of the NMDA channel pore to modify calcium permeability. This mechanism would regulate the amount of calcium influx into hippocampal neurons, which is a critical determinant of the type of plasticity (LTP or LTD) that is expressed. PKA regulation of calcium permeability can thus serve as a critical “front line” gate for controlling the strength of downstream intracellular signaling leading to induction and long-term expression of LTP. It is unclear whether this modulation of NMDAR calcium influx by PKA per se is critical for hippocampus-dependent memory, but given the established links between NMDARs, PKA, and hippocampal memory (Tsien et al., 1996; Abel et al., 1997), this idea is a testable one that will require more exact mutations of the NMDAR channel complex to selectively modify NMDAR calcium permeability in the intact animal.

AMPA receptors (AMPA Rs)

AMPA receptors (AMPA Rs) are targets of PKA (and other kinases), and PKA-mediated phosphorylation of these receptors has been implicated in the expression of hippocampal LTP. These receptors are composed of four subunits (GluR1–GluR4), which combine in different ratios to form functional receptors (Hollmann and Heinemann, 1994; Dingledine et al., 1999). Alteration of subunit compositions of AMPARs is a key mechanism for regulating synaptic strength (Liu and Cull-Candy, 2000) through control of trafficking of these receptors (Shi et al., 2001). Furthermore, reversible phosphorylation of serine residues in specific subunits is critically linked to the expression of distinct forms of synaptic plasticity. Serine residues 831 and 845, located in the intracellular C-terminal domain of GluR1, are phosphorylated by CaMKII (Barria et al., 1997; Mammen et al., 1997) and PKA (Roche et al., 1996), respectively.

The first demonstrations that PKA can regulate AMPAR currents in hippocampal neurons were accomplished by intracellular or extracellular application of modifiers of PKA activity (Greengard et al., 1991; Wang et al., 1991). AMPA/kainate receptor whole-cell currents in dissociated hippocampal neurons were potentiated by intracellular application of catalytic subunits of PKA (Wang et al., 1991), and this same treatment increased the opening frequency and open times of these channels (Greengard et al., 1991), thereby providing a molecular basis for the enhancement of whole-cell EPSC amplitudes seen following bath applications of PKA activators (Wang et al., 1991; Duffy and Nguyen, 2003).

It is noteworthy that direct infusion of membrane-impermeant PKI (a specific peptide inhibitor of PKA) into CA1 pyramidal neurons of mouse hippocampal slices blocks maintenance of LTP, and that infusion of catalytic subunits of PKA into the same CA1 neurons is sufficient to elicit long-lasting synaptic potentiation of AMPAR-mediated excitatory postsynaptic currents (Duffy and Nguyen, 2003). Also, spatial “enrichment” of mice facilitates both PKA-dependent potentiation of AMPAR-mediated synaptic responses in area CA1 and hippocampus-dependent contextual fear memory (Duffy et al., 2001), suggesting that PKA-dependent synaptic plasticity is linked to improved performance on a hippocampal memory task (cf. Abel et al., 1997).

Lee et al. (2000) have shown that induction of homosynaptic LTD in area CA1 of naïve hippocampal slices elicited dephosphorylation of serine-845 (the PKA site) of GluR1, whereas induction of LTD in previously potentiated slices dephosphorylated serine-831 (the

CaMKII site). Conversely, if LTP was induced at previously depressed synapses, serine-845 was phosphorylated, whereas LTP induction at naïve synapses elicited serine-831 phosphorylation (Lee et al., 2000). Interestingly, hippocampal learning (inhibitory avoidance performance) is associated with LTP-like increases in synaptic strength in the rat hippocampus and with GluR1 phosphorylation patterns similar to those seen after tetanus-induced LTP (Whitlock et al., 2006). These findings are consistent with the general concept that protein phosphorylation favors LTP, whereas dephosphorylation favors LTD. The results also demonstrate that different phosphorylation sites on a single receptor subunit are responsible for opposite polarities of synaptic plasticity.

AMPA receptor trafficking also plays an important role in hippocampal synaptic plasticity (Song and Huganir, 2002; Derkach et al., 2007), experience-dependent synaptic strengthening in cortical circuits (Clem and Barth, 2006), and associative learning (Rumpel et al., 2005). Recycling and sorting of AMPARs are activity-dependent, and they can be regulated by the phosphorylation state of the receptor (Carroll et al., 1999; Shi et al., 1999; Hayashi et al., 2000; Lu et al., 2001). Indeed, phosphorylation and dephosphorylation of AMPARs have been implicated in hippocampal LTD (Kameyama et al., 1998; Lee et al., 1998) and in LTP (reviewed by Soderling and Derkach, 2000), which in turn, involve the removal (Carroll et al., 1999; Man et al., 2000) or addition (Shi et al., 1999; Hayashi et al., 2000) of synaptic AMPARs, respectively. By expressing a recombinant construct of a specific subunit tagged with green fluorescent protein, Malinow and colleagues have defined some of the characteristics of AMPAR insertion (Shi et al., 1999, 2001; Hayashi et al., 2000), including a requirement for PKA-dependent phosphorylation of AMPAR subunits during synaptic plasticity (Esteban et al., 2003). The latter study showed that PKA controls the synaptic delivery of GluR4 subunits in rat hippocampal neurons, by relieving a retentive process that inhibits subunit incorporation at synapses. Interestingly, the effects of PKA are not restricted to GluR4: incorporation of GluR1, which requires CaMKII, was also blocked by inhibition of PKA (Esteban et al., 2003). Phosphorylation of serine-845 by PKA promotes AMPAR insertion and reduces AMPAR endocytosis (Man et al., 2007). More importantly, GluR1 is incorporated into synapses in a PKA-dependent manner during LTP, and stable LTP required PKA-mediated phosphorylation of serine-845 in the GluR1 subunit (Esteban et al., 2003). It should be noted, however, that ser-845 is phosphorylated under basal conditions (Lee et al., 2000); this is consistent with the observation that acute PKA activity is not necessary for induction of early stages of LTP (Huang and Kandel, 1994; but see Otmakhova et al., 2000; Yasuda et al., 2003).

In addition to AMPAR phosphorylation, AMPAR synthesis can increase several hours after L-LTP induction, and this synthesis, along with late LTP (L-LTP), were both attenuated by inhibitors of either PKA or transcription (Nayak et al., 1998). Thus, increased AMPA receptor synthesis is another mechanism by which PKA may cause L-LTP, which is known to be PKA-dependent. Overall, AMPAR incorporation at hippocampal synapses, resulting from increased synthesis and insertion, requires PKA, and it may explain the PKA-dependence of some types of LTP.

RIM1 α and presynaptic LTP

The mossy fiber (MF) pathway, which connects granule cells of the dentate gyrus to pyramidal neurons of area CA3, displays a form of LTP (MF-LTP) that is expressed presynaptically and is independent of NMDA receptor activation (for a review, see Nguyen and Woo, 2003). Activation of PKA is required for MF-LTP (Huang et al., 1994; Weisskopf et al., 1994). One presynaptic substrate for PKA during MF-LTP is RIM1 α , a presynaptic active zone protein that binds to Rab3A, a synaptic vesicle protein also implicated in MF-LTP (Castillo et al., 2002). RIM1 α knockout mice display poor MF-LTP (Castillo et al., 2002), and impaired spatial learning on the Morris water maze (Powell et al., 2004). The

presynaptic localization of RIM1 α positions it for a role in vesicular docking and fusion, processes that are logically vital for presynaptic expression of MF-LTP. Thus, MF-LTP is one form of synaptic plasticity that requires a functional interface between synaptic vesicles and active zones, mediated through binding between Rab3A and RIM1 α .

Interestingly, LTP in other brain regions also display a requirement for RIM1 α and, by inference, involvement of presynaptic PKA activation. In the cerebellum, proof that PKA phosphorylation of RIM1 α can elicit LTP was obtained by Lonart et al. (2003). LTP in RIM1 α mutant mice was rescued by presynaptic expression of RIM1 α , whereas introduction of mutant RIM1 α lacking the PKA phosphorylation site impaired LTP in wildtype neurons (Lonart et al., 2003). Also, in the Schaffer collateral pathway of CA1, genetic knockout of RIM1 α impaired L-LTP but not E-LTP, and this impairment of L-LTP may result from defective synaptic capture of gene products (Huang et al., 2005). Thus, PKA-mediated phosphorylation of RIM1 α may impact numerous processes during synaptic plasticity and possibly at multiple sites. In a broader framework, a challenge for future research is to elucidate how the pre- and postsynaptic contributions of PKA are regulated to orchestrate the multiple molecular events that underlie PKA-dependent synaptic plasticity in distinct brain structures.

CREB and CRE-mediated gene expression

Hippocampal L-LTP, but not E-LTP (early LTP), requires transcription (Nguyen et al., 1994). Activation of PKA may cause L-LTP by regulating gene expression. PKA can modify transcription by phosphorylating several different transcription factors, one of which is CREB. CREB modulates transcription of genes containing cAMP response elements (CRE) in their promoters (Montminy, 1997; Lonze and Ginty, 2002). Following stimulation that leads to an increase in cytosolic cAMP, C subunits of PKA translocate into the nucleus to phosphorylate serine-133 on CREB (Bacskai et al., 1993). This phosphorylation can initiate transcription of CRE-associated genes (Yamamoto et al., 1988; Gonzalez and Montminy, 1989).

Studies in *Aplysia* (Dash et al., 1990; Bartsch et al., 1995; Martin et al., 1997) and *Drosophila* (Tully, 1991; Yin et al., 1994) demonstrated that members of the CREB family of transcription factors are necessary for long-lasting forms of synaptic plasticity and for long-term memory. In mice, it is unclear whether CREB activation is necessary for L-LTP. Bourtchouladze et al. (1994) found that knockout of the alpha and delta isoforms of CREB impaired LTP induced by just one 100-Hz train. Balschun et al. (2003) found normal LTP induced by three trains of 100-Hz stimulation in slices from CREB mutants, and Pittenger et al. (2002) similarly found intact multi-train LTP in mice expressing a dominant negative inhibitor of CREB. Thus, the requirement for CREB in L-LTP in the mammalian hippocampus may involve regulatory mechanisms that are more complex than previously hypothesized from studies on invertebrates. Genetic backgrounds of CREB mutant mice may also play key roles in determining the synaptic phenotypes of these animals.

An important question is whether PKA-mediated activation of CREB is critical for L-LTP. Direct evidence that PKA is critical for CREB-mediated changes in gene expression that may be linked to L-LTP comes from a study by Matsushita et al. (2001), in which specific blockade of nuclear PKA activity, by targeted delivery of PKI (a specific PKA inhibitor) to the nucleus, resulted in deficient CA1 L-LTP with a corresponding reduction in CREB phosphorylation (Matsushita et al., 2001). Thus, L-LTP in area CA1 of mouse hippocampal slices involves, but may not require, CREB-mediated transcription that requires nuclear PKA activation. Furthermore, whether CREB itself, or a related CRE-binding protein, is the effector for PKA-dependent L-LTP remains to be determined as the antibodies that bind to phosphorylated CREB also recognize phosphorylated forms of closely related proteins.

Inhibitor-1 and regulation of protein phosphatase-1 (PP-1)

Protein phosphatases can interact with the cAMP signaling pathway. Activation of dopaminergic D1 receptors, which are positively coupled to cAMP production, leads to phosphorylation of DARPP-32 (dopamine and cAMP-regulated phosphoprotein, 32 kDa), an isoform of I-1 that is an endogenous inhibitor of PP-1 (Huang and Glinsmann, 1976; Hemmings et al., 1984; Greengard et al., 1999). I-1 and PP-1 have been implicated in E-LTP by studies suggesting that activation of the cAMP/PKA pathway may permit expression of E-LTP by suppressing PP-1's inhibition of E-LTP (Blitzer et al., 1995, 1998). PKA is thought to phosphorylate I-1, thereby enabling I-1 to inactivate PP-1; this would then allow E-LTP to be expressed (Blitzer et al., 1995, 1998). Indeed, stimulation that induced LTP triggered cAMP-dependent phosphorylation of I-1 and decreased PP-1 activity (Blitzer et al., 1998). Conversely, dephosphorylation of I-1 by calcineurin is thought to enable expression of LTD under conditions when calcium binding to calmodulin can activate calcineurin, which is known to be required for LTD (Mulkey et al., 1994). Calcineurin thus appears to act as an inhibitory constraint on LTP, because genetic inhibition of calcineurin enhances expression of E-LTP (Malleret et al., 2001).

The gating model of PKA/PP-1 regulation of E-LTP was also extended to L-LTP. R(AB) transgenic mice display reduced hippocampal PKA activity and deficient L-LTP in area CA1 (Abel et al., 1997; Woo et al., 2000). L-LTP in hippocampal slices from these mice was rescued by acute application of PP-1 inhibitors (Woo et al., 2002), indicating that PP-1 acts downstream of PKA to impair L-LTP. Similarly, pharmacological inhibition of PP-1 in R(AB) mutant slices also rescued forskolin-induced synaptic facilitation, which was defective in mutants (Woo et al., 2002). Interestingly, pharmacological inhibition of PP-1 had no effect on E-LTP induced by a single 100-Hz train in mutant slices (Woo et al., 2002). Thus, suppression of PP-1 by PKA selectively regulates L-LTP in mice. These collective data show that PP-1 acts as an inhibitory constraint on L-LTP, and that genetic reduction of PKA activity impairs L-LTP by enhancing this inhibitory constraint.

Some evidence indicates that I-1 is not required for hippocampal spatial learning and memory (Allen et al., 2000). Genetic knockout of I-1 did not impair performance on the Morris water maze, but it did attenuate LTP at lateral perforant path synapses (but not at Schaeffer collateral-CA1 synapses) (Allen et al., 2000). Thus, some caution is required in attributing a critical role for I-1 in specific types of hippocampal learning and memory, and not all hippocampal synapses may rely on I-1-mediated regulation of LTP.

The role of PKA in shaping the essence of memory

Our review has highlighted multiple roles for PKA in hippocampal memory. However, much remains unexplored. For example, what are the specific roles of PKA in the distinct phases of memory processing? These phases include acquisition, consolidation, reconsolidation, and retrieval of memories, and their mechanistic definitions are essential goals that must be achieved before researchers can fully grasp the essence of memory in the mammalian brain. Reversible pharmacological inactivation of hippocampal synaptic activity, by blockade of AMPAR-mediated transmission, has revealed that synaptic activity is required for encoding, consolidation, and retrieval of spatial memories in rats (Riedel et al., 1999). Reversible, genetic reduction of hippocampal PKA activity might definitively shed light on the roles of PKA in these important temporal phases of memory processing (see Isiegas et al., 2006, for evidence of PKA's inhibitory role in extinction), but more refinement is needed to achieve increasingly rapid temporal and spatial control of transgene expression to definitively resolve the contributions of PKA to the phases of memory processing.

We also need to explore the functional role of specific forms of PKA. Broadly speaking, PKA is present as RI or RII containing tetramers, referred to as type I or type II PKA respectively. These forms of PKA have different affinities for cAMP and they are localized to specific subcellular locations by AKAPs (reviewed in Bauman et al., 2004). Identifying isoform specific functions of PKA and the function of specific PKA-containing AKAP complexes is a challenge, but selective pharmacological tools are becoming available to examine these questions (e.g., Gold et al., 2006). Appropriate genetic approaches, such as the expression of specific inhibitors or the conditional mutation of appropriate genes, may also provide effective resolutions to these questions. Most of the current genetic experiments use broad-based inhibitors of either PKA activity or PKA anchoring. Identifying the specific PKA complex involved in memory storage will be critical for identifying the relevant PKA targets among the many that have been found to date.

PKA may selectively control specific aspects of memory processing. If so, this might lead to novel strategies, involving pharmacological, environmental, or genetic manipulations of PKA signaling, for alleviating memory disorders that arise from deficits of one or more of these temporal stages of memory processing. However, such strategies must be tempered by the fact that PKA activation in several brain structures, such as the prefrontal cortex and nucleus accumbens, can impair, rather than improve, cognition (Arnsten et al., 2005).

Central for further advancing our understanding of the roles of PKA in memory is the need for more research on PKA's roles in regulating synaptic plasticity in multiple brain structures. The history of this field is rich with examples of how the elucidation of mechanisms of synaptic plasticity can enhance our understanding of the cellular and molecular bases of learning and memory. Understanding the essence of memory requires a clear grasp of the integrative nature of memory processing, which involves coordinated communication between many distinct brain structures and subregions. Thus, the role of PKA in extrahippocampal synaptic physiology and cognition is ripe for future investigation. There is evidence that PKA is important for synaptic plasticity in brain regions outside of the hippocampus, such as prefrontal cortex (Jay et al., 1998), amygdala (Huang and Kandel, 1998), neostriatum (Colwell and Levine, 1995), thalamus (Castro-Alamancos and Calcagnotto, 1999), visual cortex (Hensch et al., 1998), and cerebellum (Salin et al., 1996; Chen and Regehr, 1997; Chavis et al., 1998; Linden and Ahn, 1999). Another important goal will be to distinguish between PKA's role as a *mediator*, versus its role as a *modulator*, of memory function. PKA may act as a mediator by directly controlling memory functions, whereas a modulatory role for PKA will be evident if PKA modifies the efficacies of other signaling pathways and neurotransmitter systems to alter memory dynamics.

Most, if not all, studies on hippocampal memory and synaptic plasticity are correlative because it is very difficult to establish causality between a molecular event, such as PKA activation, and a more complex process, such as synaptic potentiation or memory. At the molecular level, a critical requirement that needs to be satisfied before a definitive causal relationship between PKA activation and memory is established is direct visualization of PKA activation during memory processing. Apart from in vitro cellular imaging of PKA activity (Zhang et al., 2001; Gervasi et al., 2007), it will also be critical to refine techniques for in vivo imaging of kinase expression or activities. Such methods may be used to assess the causal relationships between PKA activity and specific behaviors, such as spatial and contextual learning. Some progress has been achieved in this domain, particularly with the emergence of two-photon imaging of neural activity in freely moving animals (Helmchen et al., 2001), but further fine-tuning is necessary to accommodate the stringent requirements for stable and specific monitoring of signal transduction in neural circuits in vivo.

Another technical approach that may yield important insights on the roles of PKA in behavior is in vivo recording of neural network activity patterns. Simultaneous recording of electrical activity in two or more interconnected brain regions in awake, freely moving animals is an important step towards elucidating the roles of identified signaling molecules in complex brain functions such as perception, learning, and memory. The relative paucity of data on multi-regional network activity patterns in genetically modified mice may now be remedied by the application of multi-electrode methods that can record oscillatory firing patterns in awake rodents, including mice (Buzsáki et al., 2003). It will be vital to apply these approaches to genetically modified PKA mutant mice (Abel et al., 1997) to directly assess the roles of PKA in regulating multi-region brain activity. Overall, the integrated application of methods from molecular and systems neuroscience will reveal novel roles for intracellular signaling in general, and for PKA signaling in particular, in learning and memory.

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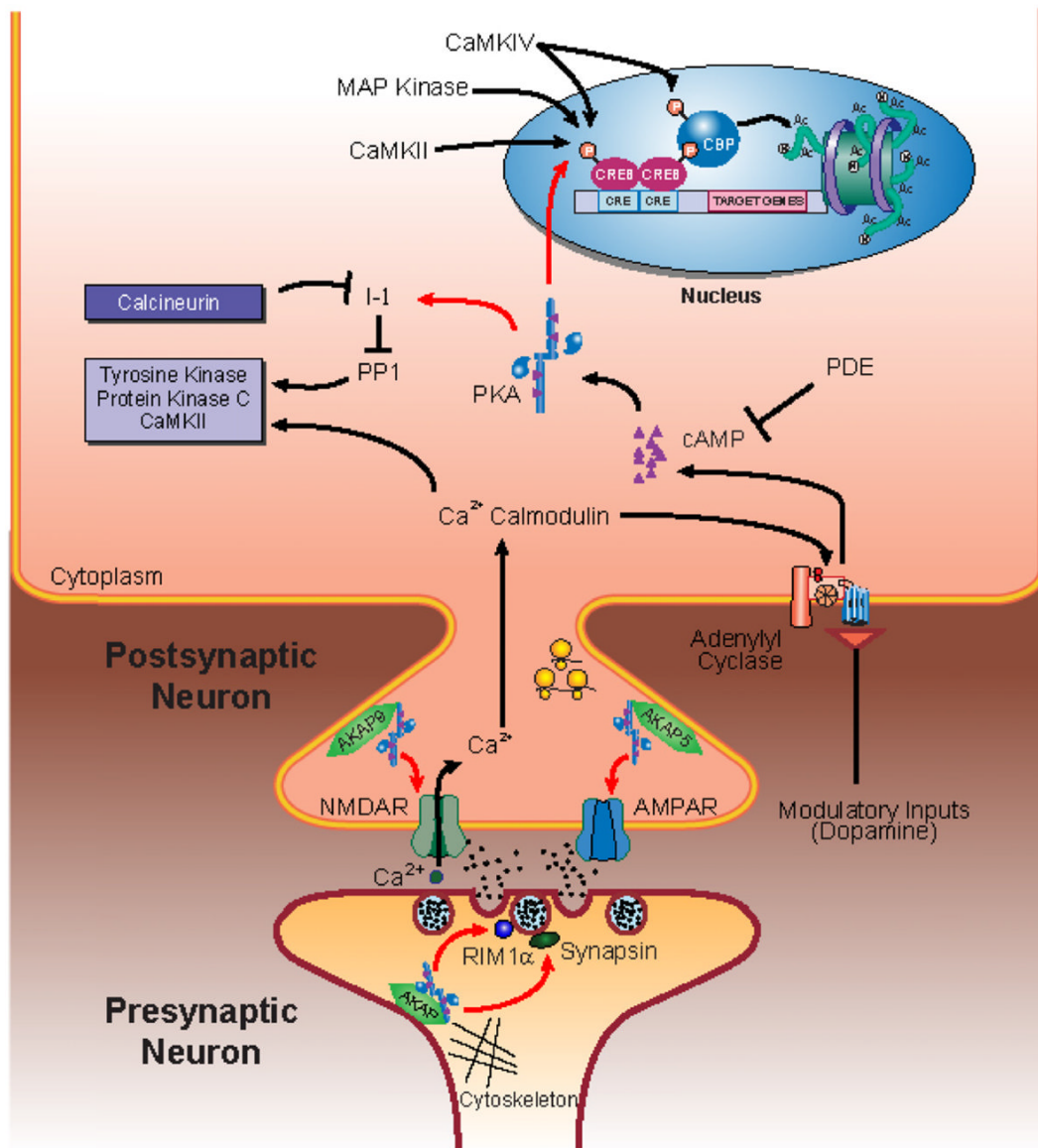


Fig. 1. The cAMP/PKA signaling pathway critically regulates molecular components underlying long-term potentiation and long-term memory. In the postsynaptic neuron, PKA targets include NMDA and AMPA receptors, inhibitor-1 (I-1) and CREB. In the presynaptic terminal, PKA targets include RIM1 α and synapsin. (See Color Plate 6.1 in color plate section.)