

PKM and the maintenance of memory

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Abstract

How can memories outlast the molecules from which they are made? Answers to this fundamental question have been slow coming but are now emerging. A novel kinase, an isoform of protein kinase C (PKC), PKMzeta, has been shown to be critical to the maintenance of some types of memory. Inhibiting the catalytic properties of this kinase can erase well-established memories without altering the ability of the erased synapse to be retrained. This article provides an overview of the literature linking PKMzeta to memory maintenance and identifies some of the controversial issues that surround the bold implications of the existing data. It concludes with a discussion of the future directions of this domain.

Introduction

Our bodies age and, barring premature death, physical decrepitude is inevitable, yet our memories can endure for a lifetime. What is the biological basis of this seemingly miraculous phenomenon? Francis Crick posed the essential question for molecular biology – “How then is memory stored in the brain so that its trace is immune to molecular turnover?” (p.101) [1]. Two generations of neurobiologists have provided a sophisticated understanding of the molecular basis of memory formation, but our understanding of how memories are maintained is still relatively primitive. Recent findings suggest, however, that Crick’s question can be answered and the memory maintenance problem can be solved.

An isoform of mammalian protein kinase C (PKC), known as PKMzeta, has been identified as playing a special role in the maintenance of memories [2]. Specifically, inhibiting the catalytic activity of PKMzeta appears to erase several types of memory in rats and mice. These results are promising but important questions about PKMzeta and its role in memory maintenance remain unanswered. In this review, I will summarize the PKMzeta hypothesis of memory maintenance, review the evidence that supports it,

and discuss the controversies surrounding the hypothesis. I will then describe data from studies of invertebrate learning and memory that indicate that PKMzeta-like isoforms of PKC are critical for memory persistence in invertebrate organisms. I conclude with a discussion of potential directions for future research regarding the role of PKMzeta and its invertebrate homologs in long-term memory.

Structure, formation, and activation of PKMzeta

PKMzeta is the autonomously active fragment of one of the so-called atypical PKCs. Full-length PKCs are grouped into three broad categories based on the second messengers that stimulate them. *Conventional* PKCs are stimulated by calcium and diacylglycerol (DAG), *novel* PKCs by DAG alone, and *atypical* PKCs by neither calcium nor DAG but, rather, by lipid factors and proteins [3,4]. Each full-length PKC consists of an N-terminal regulatory domain and a C-terminal catalytic domain linked by a hinge region. All PKCs have a pseudosubstrate in the regulatory domain; under basal conditions, the pseudosubstrate is bound to the catalytic domain, thereby keeping the enzyme inactive. Second messengers, such as calcium and DAG, bind to the regulatory domain, changing its conformation, which

removes the pseudosubstrate from the catalytic domain and permits the kinase to phosphorylate substrates. For the kinase to become fully active, however, another step is required prior to the release from autoinhibition. The "activation loop" segment of the catalytic domain must first be phosphorylated by phosphoinositide-dependent protein kinase-1 (PDK1). Phosphorylation by PDK1 converts the catalytic domain of the kinase from an inactive to an active conformation, thereby rendering the kinase catalytically competent [5]; subsequent removal of the autoinhibition by a second messenger then triggers protein phosphorylation by the PKC.

Unlike the full-length PKCs, PKMzeta lacks the regulatory domain [6,7]; therefore, once formed, the protein remains active until it is degraded. It was this feature that first suggested to Todd Sacktor, who discovered PKMzeta, that the kinase might play a key role in the maintenance of memory. Whereas PKMs were originally found through their formation by proteolytic cleavage of PKCs in the hinge region [8], Sacktor and colleagues discovered that, in the central nervous system (CNS), PKMzeta was formed by transcription from the gene for atypical PKCzeta and subsequent translation. The PKCzeta gene contains an alternative transcriptional start site that generates the mRNA for PKMzeta; once formed, the PKMzeta mRNA is transported from the nucleus to the dendrites of neurons [7]. Under basal conditions, dendritic PKMzeta mRNA is translationally repressed by its long 5'-untranslated region. Induction of learning-related synaptic enhancement, such as hippocampal long-term potentiation (LTP) [9], causes the release of the translational block on PKMzeta through activation of second messenger pathways [10,11]. Subsequent phosphorylation of PKMzeta by PDK1 then converts the kinase into a conformation with high constitutive activity [12].

Evidence for the role of PKMzeta in memory maintenance

Sacktor and colleagues provided the first evidence that PKMzeta played an important role in maintaining learning-related synaptic change. Specifically, they showed that interruption of the activity of PKMzeta disrupted the maintenance of LTP [13-15], perhaps the most prominent candidate for a synaptic mechanism of learning and memory [16-18]. Later, Sacktor and others showed that inhibiting PKMzeta also appeared to erase the long-term memory for several forms of learning as well, including spatial learning [14,19], classical conditioning of fear [19], inhibitory avoidance (a form of instrumental conditioning) [19], classically conditioned taste aversion (induced by pairing a novel taste with an emetic, commonly lithium chloride) [20,21], skilled reaching (a type of procedural learning [22]), and stimulus-response habit

formation [23]. In these studies, PKMzeta was commonly inhibited by infusing a peptide (zeta inhibitory peptide [ZIP]) having the same amino acid sequence as the pseudosubstrate of the regulatory domain of PKCzeta into the region of the CNS – hippocampus, basolateral amygdala, or insular cortex – believed to represent the site of storage for a given form of learning. Using a different approach, Shema et al. [20] showed that viral transfection of neurons in the rat insular cortex with a dominant negative mutation of PKMzeta appeared to eliminate the memory for conditioned taste aversion. These investigators also showed that overexpressing the gene for PKMzeta in insular cortical neurons one week after taste aversion training actually enhanced the taste aversion memory. Other memory-related behavioral phenomena in whose persistence PKMzeta may play a central role are neuropathic pain [24,25] and drug addiction [26-28].

How PKMzeta is believed to maintain memory

Mechanistic studies of PKMzeta and memory maintenance have focused on the effect of the kinase on the trafficking of α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid-type glutamate receptors (AMPA receptors). Movement of AMPARs into and out of postsynaptic membranes is a prominent mechanism for synaptic plasticity and learning [29]. Yao *et al.* [30] reported that trafficking of AMPARs containing the GluA2 subunit into the postsynaptic membrane is critical for the maintenance of hippocampal late-phase LTP, the persistent, protein synthesis-dependent form of LTP implicated in long-term memory [31-34]. Furthermore, Migues *et al.* [35] found that interrupting the activity of PKMzeta (through ZIP injection) in the amygdala, a structure known to be critical for fear conditioning, one day after training disrupted the maintenance of auditory fear memory; they also found that preventing the endocytotic removal of GluA2-containing AMPARs from postsynaptic sites in the amygdala (by transfecting a peptide derived from the GluA2 carboxy tail that blocks endocytosis of GluA2 subunits into amygdalar neurons) prevented ZIP-induced reversal of the fear memory. Data from a combined electron microscopic and immunohistochemical study in monkeys support the idea that PKMzeta-mediated sub-synaptic localization of GluA2-containing AMPARs is important for memory maintenance [36]. In this study, GluA2 and PKMzeta were quantified in the dendritic spines of neurons in the dentate gyrus region of the hippocampus. Monkeys with better recognition memory (as assessed by the delayed-nonmatching-to-sample, or DNMS, test) were found to possess a greater proportion of dendritic spines coexpressing GluA2 and PKMzeta. Additionally, double-labeled spines in the dentate gyrus of aged monkeys possessed a lower level of GluA2

subunits than those in the dentate gyrus of young monkeys, and this deficit correlated with poorer recognition memory in the aged monkeys.

Although the extant evidence is generally supportive of the idea that PKMzeta maintains memory through modulation of the synaptic trafficking of GluA2 subunit-containing AMPARs, a recent study indicates that PKMzeta may sometimes affect other AMPAR subunits. Shabashov *et al.* [28] reported that there is a ZIP-sensitive increase in GluA1 subunits in the nucleus accumbens shell of rats who have received cocaine-conditioned place preference (CPP) training. In contrast, however, Li *et al.* [26] concluded that ZIP injections into the nucleus accumbens core, but not the shell, disrupted the maintenance of morphine-rewarded CPP, and that injecting GluA2_{3Y} – a peptide that specifically blocks GluA2-mediated AMPAR endocytosis – into the nucleus accumbens shell eliminated the amnesic effect of ZIP on morphine-rewarded CPP. Possibly, methodological differences can explain the observed disparities in these two addiction-related studies (see [28] for discussion).

Besides an effect on AMPAR trafficking, PKMzeta's effect on the cellular substrates of memory maintenance may involve effects on neuronal structure. Overexpression of PKMzeta in cortical neurons in primary cell culture increases the proportion of spines having a stubby shape – believed to represent mature spines – and this structural alteration corresponds with an increase in the amplitude of spontaneous miniature excitatory synaptic potentials (mEPSPs) recorded electrophysiologically in the cortical neurons [37]. Such an increase in the amplitude of mEPSPs is believed to reflect an increase in mean synaptic strength. Also, overexpression of PKMzeta in hippocampal neurons in primary cell culture increases the size of clusters of postsynaptic density protein 95 (PSD-95), the major postsynaptic scaffolding protein, as well as the mean size of dendritic spines in the neurons.

To date, all of the putative PKMzeta-mediated mechanisms of memory maintenance represent postsynaptic changes. It remains to be seen whether the local activity of PKMzeta can also trigger presynaptic changes that assist in maintaining memory, such as persistent upregulation of presynaptic release. One study has reported that infusion of PKMzeta into individual hippocampal neurons does not enhance presynaptic release [13], but changes in release were only monitored for 30 minutes after PKMzeta infusion in this study; possibly, the presynaptic changes induced by upregulation of PKMzeta take longer to develop than the postsynaptic changes.

Uncertainties and controversies associated with the PKMzeta hypothesis of memory

Puzzlingly, although many forms of long-term memory do appear to be maintained by the activity of PKMzeta, others do not. For example, the expression of context-dependent fear conditioning is known to depend on circuits within the dorsal hippocampus [38]; but infusion of ZIP into the dorsal hippocampus 22 hours after training does not impair freezing by rats to a contextual conditioned stimulus, even though infusion of ZIP into the amygdala 22 hours after paired training with a tone and shock does impair freezing to the tone-conditioned stimulus [19]. Similarly, infusion of ZIP into the insular cortex does not disrupt latent inhibition of conditioned taste aversion; here, a rat is given pre-exposure to a novel taste, which is then used as the conditioned stimulus in a conditioned taste-avoidance training protocol. Prior exposure to a taste conditioned stimulus significantly attenuates later conditioned taste aversion to the same conditioned stimulus in both ZIP-treated and vehicle-treated rats [21]. Another indicator of gustatory familiarity, attenuation of taste neophobia (the unwillingness to consume food or water having an unfamiliar taste), which is produced by multiple presentations of the unfamiliar taste, is also unaffected by ZIP infusion into the insular cortex [21]. An intriguing disjunction in the effects of inhibiting PKMzeta in the dorsal hippocampus of rats has recently been reported by Hardt *et al.* [39], who found that infusing ZIP into this brain structure abolished 1-day and 6-day-old memory for the location of objects to which the animals had been exposed during training, but did not affect their long-term memory of the objects' identities. At present, there appears to be little if any underlying logic to PKMzeta's critical involvement in the persistence of some types of long-term memory, but not in others.

Another uncertainty regarding PKMzeta's role in memory maintenance concerns the permanence of the memory deficit produced by inhibiting this enzyme. The word "erasure" is commonly applied to the effect of PKMzeta inhibition on memory, which implies the elimination of the memory trace, not merely the disruption of memory retrieval. Indeed, there is ample evidence that inhibition of PKMzeta can functionally eliminate long-term memories. Perhaps the most compelling data in favor of memory erasure come from two studies by Shema and colleagues [21,40]. These investigators showed that inhibition of PKMzeta through infusion of ZIP into the insular cortex three days after conditioned taste-aversion training eliminated the avoidance of the conditioned stimulus taste for up to one month after the infusion [21]. Impressively, even when the infusion of ZIP was delayed until three months after training [40], the conditioned

response was nonetheless disrupted. Although these results indicate that even a well-consolidated memory is vulnerable to elimination by interrupting PKMzeta activity, they do not establish whether or not the physical substrate of the long-term memory is actually eradicated by PKMzeta inhibition. This is a difficult question to answer in the mammalian CNS, where identifying the set of cellular and molecular changes that underlie a specific memory is problematic.

Adding to the complexity of the PKMzeta story, some studies have found that the disruption of long-term memory produced by interruption of this kinase's activity is only temporary. A study of fear-potentiated startle reported that, whereas when tested two days after infusion of ZIP into the amygdala, a consolidated fear memory was disrupted, when tested fifteen days after ZIP infusion the memory had returned to control levels [41]. However, although apparently carefully performed, this study has generated controversy [42,43]. Also, the idea that ZIP's disruption of memory is only apparent when the test is made soon after the infusion does not accord with at least some published data [21,44].

Questions have been raised regarding the efficacy of ZIP and another inhibitor of PKMzeta, chelerythrine, used in memory erasure studies [45,46]. Specifically, it has been reported that neither ZIP nor chelerythrine inhibit PKMzeta when the kinase is expressed in mammalian non-neuronal cells in culture, or overexpressed in neurons in hippocampal slices through viral transfection [47]. The conclusions of this study have been disputed, however, on the grounds that the concentrations of ZIP and chelerythrine used to attempt to inhibit PKMzeta may not have been sufficient if the levels of exogenous PKMzeta in the expression systems used greatly exceeded those of the endogenous kinase [48].

The specificity of ZIP for PKMzeta has been another source of disagreement. ZIP has been reported to block the maintenance of hippocampal LTP and of hippocampal-dependent fear learning in PKCzeta "knockout" mice, mice in which the gene for PKCzeta has been deleted, either constitutively or conditionally [49,50]. This result suggests that there are PKMzeta-independent pathways that can mediate memory persistence. However, an alternative interpretation is that knocking out the gene for PKCzeta causes compensatory, abnormal upregulation, or enhanced phosphorylation, of a closely related PKC isoform, PKC δ [51], and that ZIP also blocks the activity of this kinase. Furthermore, in experiments on a different conditional PKMzeta knockout mouse, Tsokas *et al.* [52] found that late-phase LTP is disrupted. This group also reported that infusion of PKMzeta antisense

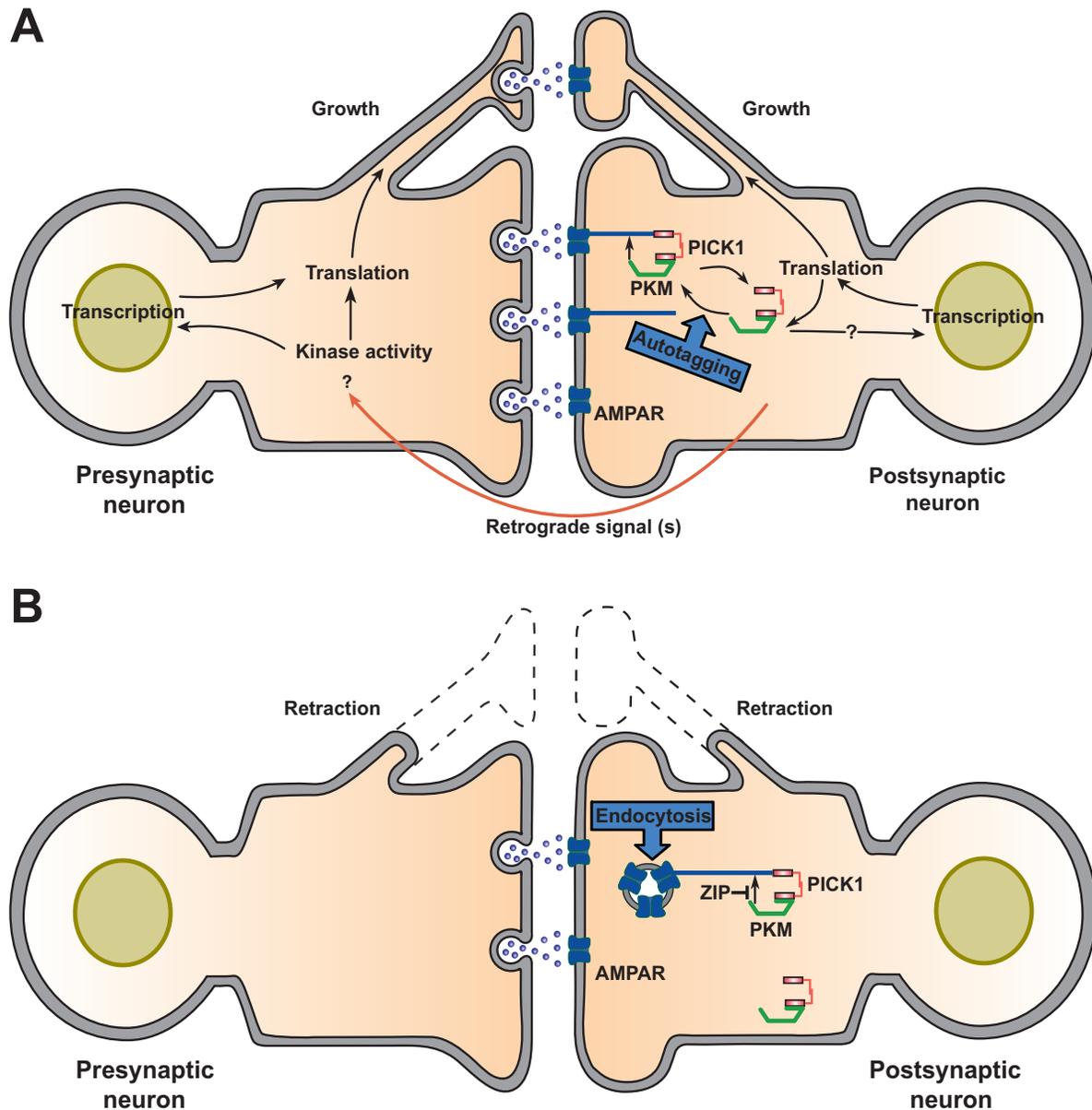
oligonucleotides into the hippocampus blocked late-phase LTP and hippocampal-dependent place avoidance learning in rats.

The technique of injecting ZIP into the intact brain to inhibit the activity of PKMzeta *in vivo* has been criticized by Lisman [53]. In one study employing this technique, ZIP was administered by injecting a 10 mM solution of the peptide into a cannula lowered into the dorsal hippocampus of rats [14]. According to Lisman, the effective concentration of ZIP in the hippocampus in this study was 100 μ M, or three orders of magnitude greater than the half maximal inhibitory concentration (IC-50) of PKMzeta; therefore, he argues, the observed disruptive effects of the peptide on memory were highly likely to have been caused by nonspecific actions of the drug. In rebuttal, Sacktor and Fenton [54] state that Lisman overestimated the concentration of ZIP in the hippocampus because he mistakenly assumed that there was continual leakage of the drug from the cannula throughout the duration of the experiment; in fact, the cannula was removed 2-3 minutes after the initial injection of the peptide. Sacktor and Fenton also point out that similar *in vivo* injections of staurosporine and H7, which effectively block CaMKII and conventional and novel PKC isoforms but not PKMzeta [45], do not impair memory maintenance, although they do disrupt original learning [14,26,40].

While recent data raise questions about the specificity of the inhibitors that have been used to block the activity of PKMzeta, it is important to keep these data in perspective in evaluating the PKMzeta hypothesis of memory maintenance. The hypothesis does not rest solely on the data from the inhibitors; data from studies using more specific techniques to alter the activity of PKMzeta, particularly expression of dominant negative constructs [4,5] and overexpression of PKMzeta in the CNS, as well as the injection of PKMzeta antisense oligonucleotides into the brain [52], significantly bolster the hypothesis.

Perhaps the most puzzling aspect of the PKMzeta hypothesis is why ZIP and chelerythrine, whose interruption of PKMzeta activity is temporary, should cause permanent disruption of long-term memories. Sacktor [2] has proposed that the answer to this conundrum lies in the concept of so-called "autotagging", whereby the activity of synaptic PKMzeta prevents its dispersion from the synapse (Figure 1.). According to Sacktor's model, when a synapse undergoes memory-related enhancement, PKMzeta increases the level of GluA2-containing AMPARs at the synapse; the extra GluA2 subunits then act as a "tag" that captures PKMzeta, together with the

Figure 1. Model of PKM's role in maintaining long-term synaptic enhancement



(a) Learning commonly involves persistent synaptic changes in the brain, indicated here by synaptic enhancement. The enhancement is mediated by both increased numbers of AMPAR-type glutamate receptors (postsynaptic change) and increased release of the transmitter glutamate from the presynaptic terminals (presynaptic change); furthermore, the presynaptic changes are shown as being triggered by one or more retrograde signals [68-70]. In addition, the synaptic enhancement involves the growth of new synaptic connections, mediated by new postsynaptic spines [71] and new presynaptic terminals [61]. The learning-related stimuli that induce the synaptic change cause local translation of PKM [7] – or cleavage of atypical PKC in *Aplysia* [56] (not shown) – which then act to insert extra AMPARs into the postsynaptic membrane [13,30]. According to Sacktor [2], the new AMPARs form a tag that maintains PKM, together with synaptic anchoring protein, the protein interacting with C kinase I (PICK1), at enhanced synapses. PKM activity, in turn, maintains the synaptic presence of additional AMPARs at the synapses. Thus, PKM activity maintains both the synaptic enhancement and the synaptic localization of the kinase (autotagging). (b) The inhibitory peptide ZIP breaks the cycle involved in synaptic autotagging, allowing the AMPARs to be dephosphorylated and endocytosed; in the absence of synaptic AMPARs, PKM is removed from the synapse, and the memory is erased. Notice that memory erasure involves physiological reversals (the removal of postsynaptic AMPARs and termination of presynaptic facilitatory processes) as well as structural reversals (retraction of spines and presynaptic terminals). The evidence that presynaptic structural changes are maintained by PKM activity is from experiments performed in *Aplysia* [72]. The figure is adapted from Sacktor [2]. Abbreviations: AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptor; PICK1, protein interacting with C kinase I; PKC, protein kinase C; ZIP, zeta inhibitory peptide.

protein interacting with C kinase (PICK1), and keeps the PKMzeta-PICK1 complex at the synapse. As long as PKMzeta is active, it continues to phosphorylate the substrate responsible for maintaining the trafficked GluA2-AMPA receptors in the synapse, thereby preventing endocytotic removal of the receptors. When PKMzeta's activity is interrupted by ZIP or chelerythrine, its substrate becomes dephosphorylated and the receptor gets endocytosed; this, in turn, allows the PKMzeta-PICK1 complex to be trafficked away from the synapse. Even when the PKMzeta inhibitor is no longer active, the synaptic enhancement cannot be reconstituted because the information about which synapses contained PKMzeta is lost. Notice that, according to this model, postsynaptically localized PKMzeta not only serves to maintain synaptic enhancement but also specifies which synapses should remain enhanced following a learning experience (the latter function is what is referred to by the term "autotagging"). It remains to be seen whether PKMzeta does indeed subserve this dual maintenance and informational role.

PKM and invertebrate memory

Homologs of PKMzeta have been identified in invertebrates. This is advantageous because the generally simpler nervous systems of invertebrates may facilitate answering some of the questions regarding PKMzeta's role in memory. A *Drosophila* homolog of PKMzeta, DaPKM, has been identified, and inhibition of this kinase blocks 24-hr memory in flies for an olfactory avoidance classical conditioning task, but does not affect original learning of the task [46]. Furthermore, over-expression of DaPKM via the induction of a transgene enhances long-term memory in mutant flies.

Recently, a homolog of PKMzeta has been isolated in the marine snail, *Aplysia*. Like its mammalian counterpart, the molluscan PKM isoform is derived from an atypical PKC, known as PKC Apl III [55]. PKC Apl III possesses a pseudosubstrate sequence in its regulatory domain that is identical to that of atypical PKCzeta. Unlike PKMzeta in the mammalian CNS, however, the *Aplysia* PKM, PKM Apl III, is formed not through translation of an mRNA but, rather, from calcium-dependent proteolytic cleavage of PKC Apl III; interestingly, this cleavage requires protein synthesis [56].

Inhibition of PKM Apl III by chelerythrine blocks the maintenance of so-called intermediate facilitation – which persists 30 minutes to 3 hours – of the synaptic connection between the sensory and motor neuron (sensorimotor synapse) produced by the facilitatory transmitter serotonin (5-HT) [57]. Moreover, expression of a dominant negative of PKM Apl III in the postsynaptic

motor neuron disrupts intermediate facilitation, but not short-term facilitation [56].

Both chelerythrine and ZIP treatment interfere with the maintenance of the memory for a form of long-term (> 24 hr) learning in *Aplysia*, long-term behavioral sensitization [58]. This form of nonassociative learning is mediated, in part, by long-term facilitation (LTF) of the sensorimotor synapse [59]. Importantly, LTF can be induced in sensorimotor cocultures by repeated applications of 5-HT, and two laboratories have now reported that the maintenance of LTF can be disrupted by either ZIP or chelerythrine [58,60]. Because a great deal is already known about the cellular and molecular substrates of long-term sensitization and LTF in *Aplysia* [61,62], the recent studies pave the way for a reductionist analysis of the mechanisms by which the activity of PKM maintains both long-term memory and long-term synaptic plasticity.

Future directions

One can anticipate that answers to many, although perhaps not all, of the present questions regarding PKM's role in memory, as outlined above, will soon be at hand. Given that this is so, what questions are likely to preoccupy neuroscientists interested in the memory maintenance in the future? PKMzeta does not appear to underlie the persistence of memory for all forms of learning. Are there other memory-maintaining molecules that function like PKM, but for different types of memory? If so, are these molecules kinases or other classes of molecules? Another interesting question is the potential role of PKM in memory phenomena that have features in common with memory erasure. Two such phenomena are memory extinction, the decline in a conditioned response due to unreinforced presentations of the conditioned stimulus [63], and memory erasure due to failure of a memory to reconsolidate after its reactivation [64-66]. Although there are significant differences among the three phenomena [67], it is possible that they involve at least some of the same underlying cellular and molecular mechanisms; indeed, some intriguing recent data have implicated PKMzeta in memory reconsolidation [27]. These and other questions raised by the discovery of PKMzeta will engage memory researchers for many years to come.

Abbreviations

AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptor; CNS, central nervous system; CPP, cocaine-conditioned place preference; DAG, diacylglycerol; DaPKM, *Drosophila* homolog of PKMzeta; LTF, long-term facilitation; LTP, long-term potentiation; mEPSPs, miniature excitatory synaptic

potential; PDK1, phosphoinositide-dependent protein kinase-1; PICK1, protein interacting with C kinase 1; PKC, protein kinase C; PKMzeta, protein kinase M zeta isoform; PSD-95, postsynaptic density protein 95; ZIP, zeta inhibitory peptide.

Disclosures

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