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The role of Cdk5 in cognition and neuropsychiatric and neurological pathology

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Abstract

Cyclin-dependent kinase 5 (Cdk5) is a proline-directed serine/threonine kinase that is ubiquitous in the nervous system and interacts with a myriad of substrates. Its modulation of synaptic plasticity and associated mechanisms of learning and memory as well as neurodegeneration and cognitive disease highlights its importance in the human brain. Cdk5 is active throughout the neuron via its kinase activity, protein-protein interactions, and nuclear associations. It regulates functions thought vital to memory and plasticity, including synaptic vesicle recycling, dendritic spine formation, neurotransmitter receptor density, and neuronal excitability. Although conditional knockout of Cdk5 improves learning and plasticity, the associated deleterious effects of increased excitability cast doubts on the therapeutic efficacy of systemic inhibitors. However, through further work on the regulation of Cdk5 and its effectors, this important molecule promises to aid in elucidating key pathways involved in learning and memory and uncover innovative therapeutic targets to treat neurodegenerative and neuropsychiatric diseases.

Keywords

Cdk5; Learning and memory; Plasticity; Neurodegeneration; Cognition

1. Introduction

Learning and memory are vital to animal development and the acquisition of modifiable, plastic neuronal circuits allows for robust adaptation to dynamic surroundings. The ability to learn from experience and employ stored knowledge in the form of memories to modify behavior in response to selective environmental pressures is crucial in animal physiology and cognition.

Where and how memories are formed and stored is a founding question in neuroscience and remains a major topic of ongoing research. Neuroscience pioneer Ramon y Cajal proposed over a century ago that mature, communicating neurons modulate the efficiency of their associations to form memories [7]. Hebb later suggested the existence of dynamic neuronal metabolism and growth that described certain forms of learning [25]. Such synaptic

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Conflict of interest

The authors declare they hold no conflicts of interest.

plasticity is supported by the neurophysiological paradigm of long-term potentiation (LTP) [5] and growing direct evidence of synaptic remodeling. As a result, an accepted theory has emerged which states that memories are formed and stored within neuronal circuits capable of modifying the strength of the synapses that connect them [50].

Numerous neurodegenerative and neuropsychiatric diseases include deficits in cognition, underscoring the importance of memory formation and recall [2]. As maladies such as Alzheimer's disease become more prevalent in the population [26], there is increasing need to unravel the pathophysiology behind them. By gaining better understanding of the mechanisms of learning and memory, we may shed light on how signaling mechanisms become dysregulated and contribute to these pathological conditions. The neuronal protein kinase Cdk5 has been implicated in regulating synaptic plasticity, learning, and memory [23]. Better understanding of the specific mechanisms by which Cdk5 mediates cognition has the potential to reveal targets for the development of new and more effective treatment strategies.

Cdk5 is a proline-directed serine/threonine kinase that modulates cortical lamination and morphology during development [21] through phosphorylating and interacting with many substrates in the mature nervous system [16]. Cdk5 may be considered to be a constitutively active kinase. Its activity is dependent upon its direct association with one of two noncyclin cofactors p35 and p39 [14,34]. These cofactors are subject to cleavage by calpain. Thus, increases in intracellular calcium, which may occur during neuronal injury or neurotoxic insult, results in conversion of p35 or p39 to p25 or p27, respectively. The resulting Cdk5/p25 or Cdk5/p27 complexes engender aberrant activity that results in deleterious effects or neuronal death, and may lead to neurodegeneration and disease [22,42].

While a number of deleterious effectors of Cdk5/p25 have been suggested to mediate neuronal injury, it is also possible that strong synaptic activity and calpain activation produces p25 locally during enhanced learning. Furthermore, the circumstances that cause Cdk5/p25 to exist in aberrant form are still unclear. For example, the kinetics of Cdk5-dependent phosphorylation of neurodegenerative targets such as tau or chromatin-associated histone H1 were shown to be unchanged *in vitro*, regardless of activation by p35 or p25 [43]. However, an earlier report [22] associated deviant Cdk5/p25 activity with pathological augmentation of its kinase actions. Either scenario does not eliminate the possibility of subcellular localization, posttranslational modifications, or protein-protein interactions playing a differentiating role in imparting aberrant activity upon Cdk5 *in vivo*.

While Cdk5 occurs throughout neurons, here we will focus on three major regions within neurons where Cdk5 function appears critical in modulating synaptic plasticity, memory, and disease. Examples of functions through which it contributes to learning are discussed. These regions, the presynaptic and postsynaptic compartments, as well as the cell nucleus, host key functions of Cdk5 and its activators (Fig. 1).

2. Presynaptic signaling

The activity of the presynaptic terminal is crucial to interneuronal communication. As the source of synaptic vesicles carrying neurotransmitters and the site of vesicle recycling, the synaptic bouton is the final output of a neuron. Therefore, any regulator of vesicle fusion or recovery at the axon terminal is a potential modifier of synaptic strength for a given stimulus and may be involved in learning and memory.

Membrane depolarization at the axonal terminal results in synaptic vesicle fusion with the plasma membrane at the synaptic cleft, and neurotransmitter release [41]. A recent study suggests that Cdk5 functions as a key control point for the modulation of neurotransmitter

release. Although the substrates involved remain unclear, this study indicates that Cdk5 activity is a major determinant in unmasking silent synapses [30].

Exocytosis at neuronal synapses is necessarily complemented by endocytosis. During gentle stimulation, vesicles are retrieved primarily via a well-described form of clathrin-dependent endocytosis (CDE), which is a relatively slow and low-capacity mechanism [20]. More robust stimulation which may occur during memory formation necessitates a distinct method of vesicle retrieval to ensure faithful signal transmission despite increased vesicle fusion and neurotransmitter release.

Activity-dependent bulk endocytosis (ADBE) monopolizes vesicle recycling during high frequency stimulation [11]. Compared to CDE, ADBE is a high-capacity process in which large portions of the membrane are pinched off, internalized, and formed into an endosome from which individual vesicles bud [48,56]. Recently, Cheung *et al.* have discovered that the vesicles produced from ADBE and CDE replenish separate pools, with the former contributing to a reserve pool that becomes activated and utilized during intense stimulation [9]. These results suggest that the differential methods of vesicle retrieval may shape how a neuron responds to future stimuli.

ADBE is dependent on a class of molecules termed dephosphins [13]. Dephosphins, including dynamin I, synaptojanin, and phosphatidylinositol phosphate kinase I γ (PIPKI γ), are necessarily dephosphorylated by calcineurin in a Ca²⁺-dependent fashion to trigger ADBE. Cdk5 rephosphorylates these dephosphins [32–33,52] and is essential for vesicle recycling and continued neurotransmitter release. Ablation of Cdk5 activity *in vivo* halts vesicle endocytosis due to lack of dephosphin rephosphorylation [52]. Evidence that Cdk5 and its physiological activator p35 are enriched in synaptosomes [53] corroborates the role of Cdk5 in the presynaptic terminal.

Cdk5 has other important substrates that control ADBE. Clayton *et al.* describe glycogen synthase kinase 3 (GSK3) as a necessary component of the phosphorylation cascade of vesicle retrieval. Interestingly, GSK3 phosphorylation of dynamin I at Ser-774 is completely dependent upon previous dynamin I phosphorylation at Ser-778 by Cdk5 [12]. The subsequent dephosphorylation of these two sites by calcineurin initiates ADBE [10].

From these reports, it appears that high-intensity stimulation induces a cycle of activity-dependent phosphorylation/dephosphorylation of dephosphins. In this sequence Cdk5 functions as a master switch that primes various components in the machinery, while the phosphatase calcineurin initiates the ADBE vesicle retrieval mechanism. Such a scheme would allow the vesicle pool of the synaptic bouton to plastically change its response to stimuli based on experience.

3. Postsynaptic signaling

Numerous signaling pathways within dendritic spines that have been implicated in plasticity and learning are regulated by Cdk5. Neurotransmitter receptors are anchored in an insoluble intracellular matrix known as the postsynaptic density. A prominent component of this key structure is the scaffold protein PSD-95, which structurally links signaling complexes to receptors. Cdk5-dependent phosphorylation of this protein inhibits multimerization and clustering with ion channels [38], thus modulating the molecular architecture of the postsynaptic terminal.

Ca²⁺/calmodulin-dependent protein kinase (CaMKII) is another constituent of the postsynaptic density involved in the synaptic remodeling that underlies learning. Cdk5 and

its cofactors interact with the α subunit of CaMKII within the postsynaptic density in a Ca^{2+} -dependent manner [15] and may regulate the activity of this kinase [27].

Cdk5 also regulates excitatory ionotropic glutamate receptors that are essential to learning. For example, Cdk5 mediates interactions between calpain and the NR2B subunit of the NMDA receptor. Conditional Cdk5 knockout in adult mice improves hippocampal-dependent learning and plasticity due to higher levels of NR2B at the synapse caused by the disruption of the calpain/NR2B complex [23]. Interestingly, the enhanced cognition and plasticity are accompanied by elevations in basal excitability and contribute to the development of epileptiform activity and audiogenic seizures [24], supporting Cdk5's role in tonal repression and baseline maintenance in neurons. Furthermore, NR2B receptor surface levels are regulated via phosphorylation of their C-terminal cytoplasmic domain by tyrosine kinases. The tyrosine phosphatase STEP hydrolyzes these phosphates and is regulated by Cdk5 [57]. Cdk5 has also been suggested to phosphorylate the NR2A subunit [35,54]. Additionally, Cdk5 may regulate the anchoring of the GluR2 subunit of the AMPA receptor via phosphorylation of the synaptic adherens junction protein δ -catenin [45].

Ionotropic glutamate receptors may mediate synaptic remodeling via Ca^{2+} -dependent signaling pathways such as those invoked via CaMKII. However, the second messenger cAMP is also essential to learning and G protein-coupled receptor (GPCR) signaling is modulated by Cdk5. For example, Cdk5 regulates the protein phosphatase-1 inhibitors DARPP-32 [4] and inhibitor-1 [3,39], both of which are activated by cAMP/PKA and have been implicated in postsynaptic plasticity mechanisms [8,36]. Unpublished findings from our laboratory indicate that Cdk5 regulates cAMP-dependent signaling at multiple steps and may maintain a baseline tonus through these pathways in a manner that might be considered analogous with its presynaptic function.

In response to synaptic firing, localized conversion of p35 to p25 may redirect the kinase from its subcellular localization with membranous or cytoskeletal components, thereby removing its tonic regulatory influence on synaptic pathways. This remains to be determined and the functions of p25 in plasticity are presently unclear. Evidence indicates that Cdk5/p25 contributes to the loss of mitochondrial integrity [37]. Cdk5/p25 could influence mitochondrial translocation at active synapses, for example, through the phosphorylation of proteins such as the dynamin-related GTPase Drp1 that are targeted during mitosis by Cdk1 [51].

While the list of postsynaptic Cdk5 substrates is growing, understanding of its regulation remains incomplete. Although conditional Cdk5 knockout has proven to be a useful tool to study the function of Cdk5 in cognition, few selective inhibitors such as CP-681301 [55] and Indolinone A [18] have become readily available and appear ineffective systemically in our laboratory. The development of cell-specific Cdk5 conditional knockouts, systemic inhibitors with strong pharmacokinetic properties, and new strategies to selectively target specific Cdk5 signaling pathways will lead to important advances in understanding the regulation and function of Cdk5 in learning and memory mechanisms.

4. Nuclear signaling

More recently, Cdk5 has been connected to the regulation of neuronal gene transcription. This modulation of gene and protein expression provides a mechanism through which Cdk5 may produce long lasting changes in neuronal architecture, excitability, and viability. Because Cdk5, to our knowledge, has never been shown to be mutated in a pathological state, its effects in the nucleus could explain associations between wild-type Cdk5 and neurodegenerative insults such as Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, and ischemia.

Alteration of histone acetylation is a critical part of chromatin remodeling and hence gene transcription [47]. Histone deacetylase 1 (HDAC1) action in gene promoter regions condenses chromatin, impedes access of transcription factors, and suppresses transcription [6]. Kim *et al.* have shown that p25-expressing transgenic mice undergo HDAC1 inactivation in a Cdk5-dependent manner [29]. How Cdk5 inactivates HDAC1 remains to be seen, but it is clear that this inactivation leads to abnormal cell cycle activity, DNA damage, and neuronal death [29]. Future studies may expand the association between HDACs and Cdk5 and the role of these pathways in the formation of memory.

Cdk5 maintains other links within the nucleus. The transcription factor myocyte enhancer factor 2 (MEF2) is a pro-survival signal in neurons which reduces interneuronal connections by decreasing the number of dendritic spines in an activity-dependent fashion [17]. This synaptic pruning which is paramount in the maturing nervous system is diminished in several conditions including fragile X syndrome, a common form of inherited mental retardation and autism [28]. Cdk5 inhibits MEF2 by phosphorylating residue Ser444 [19], such that under calpain-induced p25 production, dopaminergic striatal neurons are lost in a mouse model of Parkinson's disease [49]. Loss of fragile x mental retardation protein in fragile X syndrome eliminates synaptic pruning via MEF2-activated targets [44]. Inhibition of MEF2 via Cdk5/p25 may create a condition of numerous inappropriate excitatory connections that would typically be eliminated by MEF2 pruning, leading to mental impairments and autistic phenotypes.

Nuclear and epigenetic mechanisms controlling learning and memory may also contribute to the etiology of neuropsychiatric disorders such as addiction which have strong cognitive components. For example, increases in Cdk5-dependent inhibitory phosphorylation of MEF2 may contribute to increases in synaptic spine density in response to chronic cocaine exposure [46]. This neuroadaptive morphological effect is dependent upon Cdk5 activity [40] and Cdk5 itself serves as an epigenetic target of cocaine via the invocation of the Δ FosB transcription factor [1,31].

5. Conclusions

Cdk5 is essential to learning and memory in the adult brain and has the ability to affect many neuronal divisions, including the pre- and postsynaptic compartments and the nucleus. For example, as a governor and primer of ADBE, Cdk5 augments plasticity presynaptically. By facilitating the proteolysis of NMDA receptor subunits postsynaptically, it functions to modulate excitability and synapse strengthening. Epigenetically, deregulated Cdk5 can lead to transcription of genes that affect dendritic spine number and induce memory deficits. Unlike other protein kinases involved in plasticity, Cdk5 is constitutively active and the dephosphorylation of its substrate sites in response to Ca^{2+} conductance may take precedence over its directed holoenzyme activity in mediating synaptic remodeling.

Regulatory mechanisms controlling Cdk5 activity remain unclear, but the relationship between the physiological function of Cdk5 in cognition and its contribution to neuronal injury and death is palpable. A reasonable hypothesis linking Cdk5 and synaptic plasticity is that the machinery of the cell cycle was adopted to serve synaptic remodeling, allowing the conversion of naïve synapses to form strong connections, and thereby recording experiences within neuronal circuits. Cdk5 may be the adaptive product of CNS evolution, but its neurotoxic potential may lie within its vestigial cell cycle-like nature.

Cdk5 reduction enhances cognition and systemic drugs that inhibit its activity have been considered as a therapeutic strategy for neurodegenerative diseases. However, the consequence of its essential role in cognition may be that targeting its enzymatic activity

produces unacceptable side effects. While this may reduce the enthusiasm for Cdk5 drug discovery, it is important to note that there may be very high therapeutic value in inhibiting Cdk5 acutely during neuronal injury such as that associated with stroke or traumatic brain injury, or when risk is high such as during protracted labor or during cardiovascular or neurovascular repair surgeries. For other neurological or neuropsychiatric diseases, selectively targeting specific regulatory pathways or blocking excessive aberrant activity may be an effective alternative to explore.

Since its discovery, Cdk5 has been found to be essential to CNS function and its role in peripheral tissue and disease is growing. As our understanding of its role in cognition continues to expand, Cdk5 will likely prove to be a powerful and focused tool in profiling behavioral and disease states. The knowledge gained from the study of Cdk5 will lead to new perspectives and deeper comprehension of the key pathways involved in memory and novel therapeutic approaches for neurological and neuropsychiatric disorders.

Abbreviations

ADBE	activity-dependent bulk endocytosis
CaMKII	Ca ²⁺ /calmodulin-dependent protein kinase
CDE	clathrin-dependent endocytosis
Cdk5	cyclin-dependent kinase 5
GSK3	glycogen synthase kinase 3
HDAC1	histone deacetylase 1
LTP	long-term potentiation
MEF2	myocyte enhancer factor 2
PIPKIγ	phosphatidylinositol phosphate kinase I γ

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Fig. 1.

Summary of several key molecules linked to synaptic plasticity with which Cdk5 interacts. In the presynaptic compartment, Cdk5 modulates the dephosphorylated dynamin I, amphiphysin I, and PIPKI γ as well as GSK3 to affect synaptic vesicle retrieval and priming. In the postsynaptic compartment, Cdk5 interacts with molecules controlling cytoskeletal architecture and receptor density, including NR2B, PSD-95, CaMKII, STEP, and DARPP-32. In the nucleus, Cdk5 interacts with HDAC1 to influence gene expression epigenetically and MEF2 to inhibit neuronal pruning.