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Review

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.

Contents

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 Ramón 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 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

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 Iγ.

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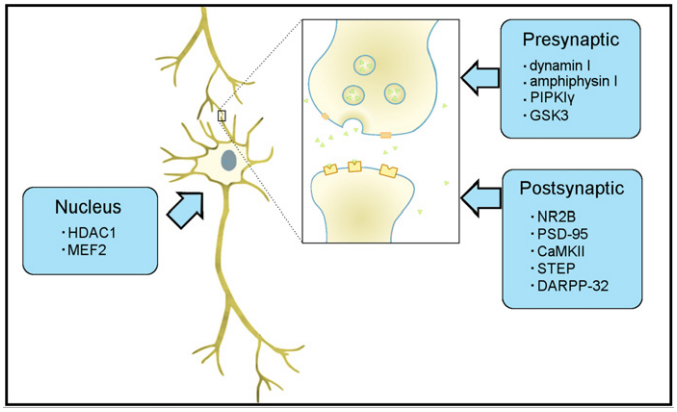

Fig. 1. Summary of several key molecules linked to synaptic plasticity with which Cdk5 interacts. In the presynaptic compartment, Cdk5 modulates the dephosphins dynamin I, amphiphysin I, and PIPKIγ as well as GSK3 to affect synaptic vesicle retrieval and priming. In the postsynaptic compartment, Cdk5 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.

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 Iγ (PIPKIγ), are necessarily dephosphorylated by calcineurin in a Ca^{2+}-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.