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Review

Recent advances in understanding the roles of Cdk5 in synaptic plasticity

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ABSTRACT

The molecular composition of the postsynaptic density is modified during synaptic plasticity, which forms the molecular basis of learning and memory. Such changes in synaptic composition depends in part on the intricate regulation of phosphorylation of specific proteins via different protein kinases, including a serine/threonine kinase, cyclin-dependent kinase 5 (Cdk5). However, the mechanisms underlying the involvement of Cdk5 in neural plasticity remain elusive. Recently, the identification of a number of synaptic proteins as substrates or interacting proteins with Cdk5 provides important clues on how this kinase modulates the efficacy of synaptic transmission. In this review, we summarize the recent findings to illustrate the multi-faceted roles of Cdk5 in synaptic plasticity through affecting dendritic spine formation, ion channel conductance, protein expression, and transcription in the postsynaptic neurons. Importantly, dysregulation of Cdk5 has been linked to Alzheimer's disease, which involves perturbations in synaptic functions and memory formation. Understanding the mechanisms by which Cdk5 regulates synaptic plasticity may therefore provide important insights in the design of novel therapeutic strategies for neurodegenerative diseases.

1. Introduction

Synaptic plasticity, in which the efficacy of neurotransmission is modulated by experience, is believed to underlie memory formation and higher cognition in the nervous system. It involves structural and functional modification of the postsynaptic density by synaptic activity, and depends on the intricate regulation of protein localization, gene transcription, protein synthesis and protein degradation. How this large array of different cellular events is regulated by synaptic activity has been a central question for the study of synaptic plasticity. One crucial means of regulating these cellular processes involves phosphorylation of synaptic proteins by protein kinases.

The serine/threonine kinase Cdk5 and its activator p35 play multiple roles during nervous system development [1]. Emerging evidence suggests that they are also involved in synaptic plasticity in mature neurons [2,3]. First, both Cdk5 and p35 are localized at neuronal synapses as well as the neuromuscular junction [4–6]. Second, many synaptic proteins isolated from the synaptosomes of adult brains are putative substrates of Cdk5 [7]. Finally and most importantly, the induction of synaptic plasticity, as well as hippocampus-dependent spatial learning, is affected in Cdk5 and p35 transgenic and knockout mice [8].

The role of Cdk5 in synaptic plasticity and learning was initially studied using the Cdk5 inhibitors roscovitine and butyrolactone I, which inhibited LTP induction in the area CA1 of hippocampus and context-dependent fear conditioning, respectively [9,10]. The significance of Cdk5 in synaptic plasticity and hippocampus-dependent spatial learning was further demonstrated by studies using knockout and transgenic animals. Long-term depression and spatial learning were impaired in p35 null mice [11]. Studies on these mice and, more recently, Cdk5 conditional knockout mice further reveal that Cdk5 is not absolutely required for the induction and expression of LTP, but rather plays a modulatory role by increasing the threshold for LTP induction [12,13]. Spatial learning is enhanced in the Cdk5 conditional knockout mice, in which the expression of Cdk5 is substantially lowered when compared to that of wild-type animals [13]. The increased induction threshold for LTP by Cdk5 is consistent with the observation that expression of p35, and hence Cdk5 activity, is down-regulated by theta burst stimulation during the induction of LTP [12]. The interpretation of the role of Cdk5 in synaptic plasticity and spatial learning is complicated by studies revealing that transgenic mice transiently expressing p25, which is the cleaved product of p35, also show enhanced LTP and spatial learning [14–16]. One proposed explanation is that p25 might enhance synaptic plasticity and learning by disrupting the interaction between Cdk5 and p35, which in turn reduces degradation of the NR2B subunit of NMDA receptor [8].

In line with the studies on the role of Cdk5 in synaptic plasticity and learning, numerous studies in recent years have identified novel substrates and interacting proteins of Cdk5 in neurons, some of which provide significant insights into the mechanisms of how Cdk5 is involved in modulating synaptic plasticity. We summarize below those studies demonstrating a potential link between Cdk5-mediated phosphorylation and the functioning of the postsynaptic compartment, and in some cases how it is regulated by neuronal activity. The activity-dependent phosphorylation by Cdk5 might underlie the

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induction and expression of neural plasticity, including Hebbian forms of synaptic plasticity and homeostatic response to different stimuli such as chronic elevation of synaptic activity or repetitive exposure to cocaine. Potential Cdk5 substrates include pre- and postsynaptic proteins, suggesting that Cdk5 likely regulates the functioning of both the presynaptic terminal and the postsynaptic apparatus. Here, we mainly focus on how Cdk5 might regulate synaptic transmission on the postsynaptic neurons. There are excellent reviews on the phosphorylation of presynaptic proteins by Cdk5 and its potential role in neural plasticity [e.g. 8,17], and will not be elaborated in this review.

2. Cdk5 and dendritic spine formation

Given the large number of cytoskeleton-binding proteins as Cdk5 substrates in neurons, it is perhaps not surprising that one potential mechanism underlying the ability of Cdk5 to modulate synaptic plasticity involves regulation of dendritic spine formation (Fig. 1). Dendritic spines are specialized postsynaptic compartments where excitatory transmission takes place, and can be modified by synaptic activity [18]. Changes in dendritic spine morphology depend on signaling that regulates organization of the actin cytoskeleton [19,20]. The F-actin-binding protein spinophilin, which is enriched at dendritic spines and negatively regulates their formation [21], and its related protein neurabin I can both be phosphorylated by Cdk5 [22,23]. The functional consequence of their phosphorylation by Cdk5 on spine formation remains to be determined.

The Rho family of small GTPases consists of important signaling molecules that relay signals to the actin cytoskeleton in response to extracellular stimuli [24]. We recently found that the Rho guanine nucleotide exchange factor (GEF) ephexin1 is phosphorylated by Cdk5 and this phosphorylation is critically involved in dendritic spine retraction in response to ephrinA1, the cognate ligand that activates the receptor tyrosine kinase EphA4 [25]. Activated EphA4 recruits Cdk5, phosphorylates Cdk5 at Tyr-15 and increases its kinase activity. The active Cdk5 in turn phosphorylates ephexin1, which activates RhoA and results in retraction of dendritic spines in response to stimulation by ephrinA1 [25]. Notably, EphA4 was recently shown to be required for synaptic plasticity in the amygdala [26], raising the possibility that the EphA4–Cdk5–ephexin1 pathway may be crucial in regulating spine density during synaptic plasticity.

Another potential candidate that mediates dendritic spine plasticity in response to synaptic activity is the Wiskott–Aldrich syndrome protein (WASP)-family verprolin homologous protein 1 (WAVE1). WAVE1 is crucial for dendritic spine formation in the striatum, as indicated by abnormal spine formation in WAVE1 knockout mice [27]. WAVE1 regulates actin polymerization and thereby dendritic spine formation through its interaction with the Arp2/3 complex, and that interaction is suppressed upon phosphorylation by Cdk5 [27]. Interestingly, repetitive depolarization of hippocampal neurons induced WAVE1 dephosphorylation at the three Cdk5 phosphorylation sites [28]. The same study also showed that WAVE1 is required in the increased spine formation after neuronal depolarization. Since depolarization and the subsequent activation of NMDA receptor is required for the induction of Hebbian-LTP, these studies raise the interesting possibility that down-regulation of Cdk5 activity and dephosphorylation of WAVE1 may represent an important mechanism underlying increased spine density observed after LTP induction.

Activation of Cdk5 does not always suppress spine formation. Chronic exposure to cocaine induces Cdk5 activity in a subpopulation of neurons in the nucleus accumbens *in vivo*, leading to phosphorylation and repression of the transcription factor MEF2, thereby enhancing dendritic spine formation (see below). Transient expression of p25 in the forebrain of transgenic mice, which elevates Cdk5 kinase activity, also increases spine density *in vivo* [16]. In addition, the tubulin-binding protein collapsing response mediator protein 1 (CRMP1) can be phosphorylated by Cdk5 at Thr-509 and Ser-522, and the phosphorylation of CRMP1 is crucial for dendritic spine formation in response to semaphorin3A [29]. Whether phosphorylation of CRMP1 by Cdk5 is involved in activity-dependent regulation of dendritic spine formation requires further investigation. Finally, we recently found that TrkB, the receptor of the neurotrophin BDNF, can be phosphorylated by Cdk5, which is crucial for BDNF-induced outgrowth of dendrites in hippocampal neurons [30]. Since BDNF-TrkB signaling is involved in the growth and maturation of dendritic spines [31,32], it will be interesting to further explore if Cdk5 also mediates the effect of TrkB on spine morphogenesis.

3. Cdk5 and NMDA receptor

NMDA receptor acts as the sensor for coincident pre- and postsynaptic neuronal activity, and is therefore critical to both Hebbian-LTP and LTD. The functional NMDA receptor is a heteromeric complex composed of the NR1 subunit and one or more of the regulatory NR2 subunits. Phosphorylation of NR1 and NR2 subunits regulates channel properties and localization [33]. Cdk5 phosphorylates NR2A at Ser-1232, and the NMDA-evoked current in hippocampal neuron is reduced by roscovitine, suggesting that the conductance of NMDA receptor may be regulated after phosphorylation by Cdk5 [9]. This was confirmed by the observation that recombinant NMDA receptor current is increased by co-expressing Cdk5 and p35 in HEK293 cells, and the enhancement is abolished

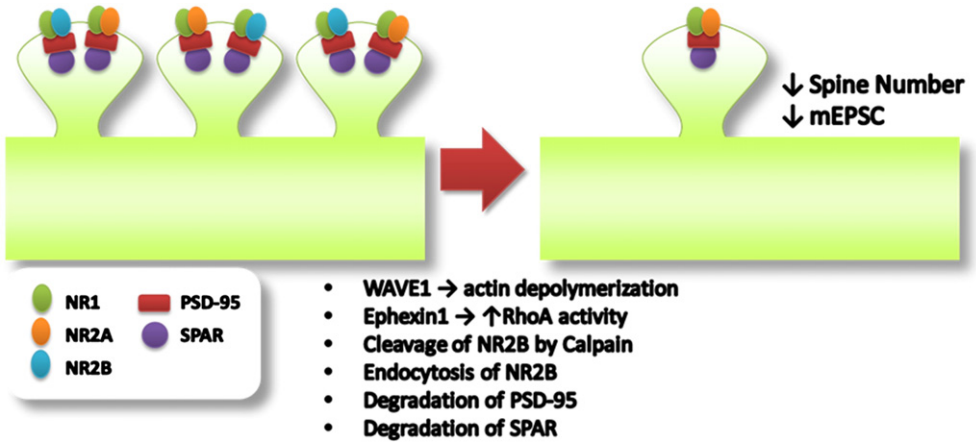

Fig. 1. Possible mechanisms underlying the effect of Cdk5 on dendritic spine elimination and reduction of mEPSC. Cdk5 acts on the Rho GEF ephexin1 and the actin-binding protein WAVE1 to trigger retraction of dendritic spines. Cdk5 also promotes the cleavage and endocytosis of the NR2B subunit of NMDA receptors, as well as degradation of the postsynaptic scaffold proteins PSD-95 and SPAR. All these changes are anticipated to lead to reduced synaptic transmission.

upon mutation of Ser-1232 of NR2A [34]. Cdk5 can also indirectly modulate NMDA-evoked EPSC in the striatum through its effect on dopamine release. Unlike what was observed in hippocampal neurons, inhibition of Cdk5 activity by roscovitine enhances NMDA-EPSC in striatal neurons by increasing the phosphorylation of NR1 at Ser-897, and this process requires presynaptic dopamine and post-synaptic DARPP32 [35]. Since the dopamine level is low in the hippocampus when compared to the striatum [35], it is likely that Cdk5 mainly acts on NR2A instead of NR1 in the hippocampus, which will account for the reduced NMDA current by roscovitine [9].

Cleavage by specific proteases such as calpain modulates the expression level of synaptic proteins, including the NR2B subunit of NMDA receptor, during neural plasticity [36]. The enhanced LTP and spatial learning observed in Cdk5 conditional knockout mice can be attributed to reduced degradation of the NR2B subunit of NMDA receptor [13]. NMDA induces calpain-mediated cleavage of NR2B, which is perturbed in brain slices prepared from Cdk5 conditional knockout mice. The resulting higher expression of NR2B reduces the threshold of LTP induction, as indicated by the ability of NR2B-selective inhibitor ifenprodil to block the enhanced LTP observed in Cdk5 knockout slices [13]. This study therefore suggests that Cdk5 mainly acts on NR2B, instead of NR2A, to modulate the threshold for LTP induction. Interestingly, the effect of Cdk5 on the cleavage of NR2B by calpain does not depend on its kinase activity. Rather, Cdk5 forms a complex with calpain and NR2B and thereby promotes the cleavage of NR2B [13]. Apart from calpain-mediated cleavage, Cdk5 also regulates the endocytosis of NMDA receptor via phosphorylation of PSD-95. Inhibition of Cdk5 increases the binding of PSD-95 to the tyrosine kinase Src, which in turn induces phosphorylation of NR2B at Tyr-1472, and attenuates activity-induced endocytosis of NR2B [37]. These two studies therefore collectively show that reduced Cdk5 expression or inhibition of Cdk5 activity leads to higher expression of surface NR2B by reducing NMDA-dependent degradation and endocytosis (Fig. 1).

The scaffolding proteins that anchor NMDA receptors to the postsynaptic density can also be directly phosphorylated by Cdk5. For example, PSD-95 was identified as a substrate of Cdk5, with the phosphorylation sites located at the N-terminus of PSD-95 (Thr-19, Ser-25, and Ser-35). Mutation of these residues to alanine resulted in the appearance of large PSD-95 puncta in immunofluorescence, which is similarly observed in hippocampal neurons cultured from Cdk5 null mice, suggesting that Cdk5 negatively regulates PSD-95 clustering [38]. Finally, Cdk5 may also regulate the degradation of PSD-95 and its interacting protein SPAR at the postsynaptic density [39,40]. Cdk5 can therefore indirectly modulate the function of NMDA receptor through regulating the expression of scaffold proteins.

4. Cdk5—signaling to the nucleus

While most studies on Cdk5 signaling in neurons are focused on the ability of this kinase to regulate cytoskeleton dynamics, ion channels, and other protein kinases and phosphatases, relatively little was known about its role in mediating long-lasting changes in neurons that depend on gene transcription. Emerging studies, however, have identified various nuclear proteins as potential Cdk5 substrates (Fig. 2), thereby raising the possibility that Cdk5 is involved in modulating transcription in the nucleus that is required in long-term synaptic plasticity.

The involvement of Cdk5 in regulating transcription that leads to long-lasting changes in neural plasticity is perhaps best illustrated during chronic exposure to cocaine. Repeated cocaine treatment induces Cdk5 activity in a subpopulation of neurons in the nucleus accumbens via increased expression through the transcription factor delta FosB [41,42]. Induction of Cdk5 activity leads to phosphorylation and reduced activity of the transcription factor MEF2, which results in the growth of dendritic spines [43–45]. Expression of constitutively active MEF2 in the nucleus accumbens abolishes the increased spine density in response to chronic cocaine treatment, and unexpectedly enhances behavioral sensitivity to cocaine [45]. The MEF2-dependent increase in spine density might therefore represent a compensatory response to chronic cocaine exposure, rather than being required in cocaine sensitization. Nonetheless, these studies clearly demonstrate that Cdk5 can signal to the nucleus to regulate gene expression that is essential for structural changes at the synapses, and ultimately leads to long-lasting behavioral plasticity.

Our laboratory has identified several nuclear proteins as Cdk5 substrates, including Stat3 and mSds3 [46,47]. Stat3 is a well established transcription factor that regulates transcription in response to many different cytokines [48]. Cdk5 phosphorylates Stat3 at Ser-727 in muscle after activation of ErbB receptor by neuregulin, which enhances the DNA binding and transcription of downstream target genes [46]. Notably, both Cdk5 and Stat3 are implicated in the pathogenesis of Alzheimer's disease, since the expression of β-secretase BACE1, which cleaves amyloid-β precursor protein (APP) to generate plaque-associated Aβ, is promoted by Stat3 in a Cdk5-dependent manner [49]. Recent studies from our laboratory found that Stat3 can also be activated by other receptor tyrosine kinases such as EphA4 and Trk receptor [50,51]. Interestingly, all these receptor tyrosine kinases have been shown to modulate dendritic spine formation and synaptic plasticity [2]. It is therefore important to examine if Stat3 is also involved in modulating synaptic functions in mature neurons.

mSds3 is a co-repressor of mSin3-histone deacetylase (HDAC). The repressor activity of mSds3 increases after phosphorylation at Ser-228 by Cdk5 [47]. While the stimulus that triggers this phosphorylation is not clear, mSds3 is abundant in adult brain [47]. It is noteworthy that synaptic activity might regulate transcription by modulation of chromatin via acetylation and deacetylation of histone in the nucleus [52]. With the emerging evidence for the significance of chromatin remodeling in learning [53], it will be of great interest to examine whether Cdk5-mediated phosphorylation of mSds3 can be regulated by synaptic activity in mature neurons, and to explore its significance in transcription-dependent long-term synaptic plasticity.

Considering the hypothesis that Cdk5 can signal to the nucleus to modulate long-term plasticity via transcriptional regulation, one interesting question is how Cdk5, which presumably is localized at

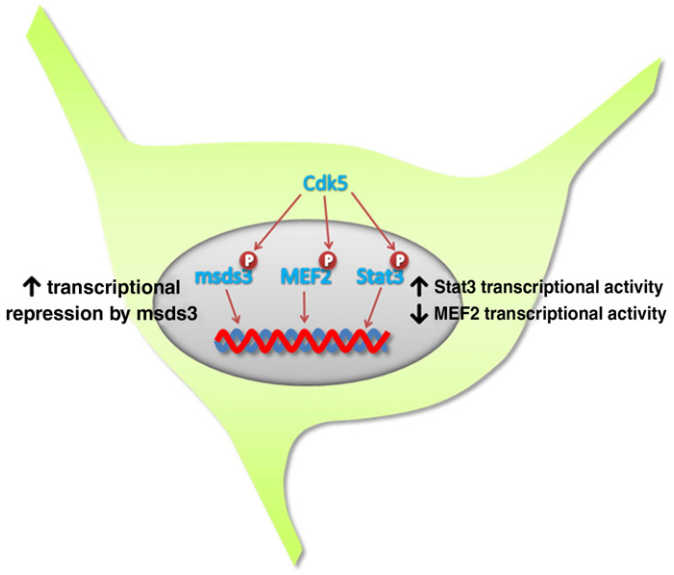

Fig. 2. Cdk5 can signal to the nucleus to regulate gene transcription. The transcription factors MEF2 and Stat3, and the transcriptional repressor mSds3, can be phosphorylated by Cdk5, after which their activities are regulated. The roles of these transcription factors in neuronal plasticity remain to be determined.

synapses away from the cell soma, relays the signals to the nucleus. One possibility is that Cdk5 and its activator p35 can be transported retrogradely along the dendrite and translocated into the nucleus, where Cdk5 phosphorylates its substrate such as MEF2. Nuclear localization of Cdk5 and p35 has been reported in neurons [54], and p35 can move into the nucleus through the nuclear import carrier importin-beta [55]. In addition, nuclear Cdk5 activity is crucial for neuronal apoptosis [43,56]. It is therefore plausible that neuregulin, BDNF, or synaptic activity might regulate various transcription-dependent processes in neurons by triggering the nuclear import of Cdk5 and p35. Cdk5 may also regulate gene expression through p25, which is known to be present in the nucleus and has been implicated in synaptic plasticity. Alternatively, Cdk5 may phosphorylate its substrates at the synapses, which then triggers the retrograde movement and nuclear import of the substrates, rather than Cdk5 itself, into the nucleus. This hypothesis is consistent with the findings that a number of transcription factors are localized in distal processes and synapses, and their retrograde trafficking and nuclear import is triggered by stimuli that produce long-term synaptic plasticity [57,58].

5. Conclusions and future directions

Through the identification of different substrates for Cdk5 in neurons, significant progress has been made in recent years in understanding how Cdk5 might regulate the function and expression of postsynaptic proteins. Cdk5 phosphorylation is involved in modulating the conductance and expression of NMDA receptors, formation and retraction of dendritic spines, degradation of synaptic proteins, and signaling to the nucleus to modulate gene expression. All these molecular changes might contribute to the altered synaptic plasticity observed in Cdk5 or p35 knockout mice. Identification of more Cdk5 substrates will undoubtedly increase our understanding of the mechanisms underlying the role of Cdk5 in synaptic plasticity. It is equally important, however, to examine how the Cdk5 phosphorylation of various substrates is regulated in different forms of neural plasticity. Finally, it is crucial to investigate if the resulting Cdk5-mediated phosphorylation of different proteins is required in the induction or expression of different forms of neural plasticity by introducing Cdk5 phosphorylation deficient or mimicking mutants into neurons.

It is clear that the roles of Cdk5 in synaptic plasticity are multi-faceted. For example, Cdk5-mediated phosphorylation of different proteins can lead to opposing consequences in dendritic spine formation, i.e. phosphorylation of WAVE1 and ephexin1 results in the loss of dendritic spines, whereas increased spine density is observed after phosphorylation of CRMP1 and MEF2. Similarly, activation of Cdk5 increases the degradation of PSD-95 and SPAR, but also reduces activity of ubiquitin ligase and its activator [59]. One possible explanation is that different subsets of substrates are phosphorylated by Cdk5 in response to different extracellular stimuli, e.g. ephrinA induces spine retraction via phosphorylation of ephexin1 by Cdk5, whereas semaphorin3A triggers Cdk5-dependent phosphorylation of CRMP1 that leads to spine formation. With regard to synaptic plasticity, it is especially important to understand how Cdk5 activity is regulated upon activation of NMDA receptor. Glutamate has been shown to induce transient activation of Cdk5, which is followed by ubiquitin-mediated degradation of p35 and thereby down-regulation of Cdk5 activity [12]. NMDA receptor is involved in both LTP and LTD, which have opposite consequences in spine density [18]. If Cdk5 is indeed involved in both processes in regulating the formation of dendritic spines, the prediction will be that Cdk5 is differentially regulated during the induction of LTP and LTD, and different subsets of proteins are phosphorylated, ultimately leading to opposite changes in spine density.

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