Chapter 3
Interaction of Cdk5 and cAMP/PKA Signaling in the Mediation of Neuropsychiatric and Neurodegenerative Diseases

Yafang Hu, Suyue Pan, and Han-Ting Zhang

Abstract Both cyclin-dependent kinase 5 (Cdk5) and cyclic AMP (cAMP)/protein kinase A (PKA) regulate fundamental central nervous system (CNS) functions including neuronal survival, neurite and axonal outgrowth, neuron development and cognition. Cdk5, a serine/threonine kinase, is activated by p35 or p39 and phosphorylates multiple signaling components of various pathways, including cAMP/PKA signaling. Here, we review the recent literature on the interaction between Cdk5 and cAMP/PKA signaling and their role in the mediation of CNS functions and neuropsychiatric and neurodegenerative diseases.

Keywords cyclin-dependent kinase 5 • cyclinc AMP • protein kinase A

3.1 A Brief Introduction

Cyclin-dependent kinase 5 (Cdk5) and cyclic AMP (cAMP)/protein kinase A (PKA) signaling are two extensively studied and important mediators in fundamental central nervous system (CNS) functions. Accumulating evidences suggest crosstalk between Cdk5 and cAMP/PKA signaling in several physiological and disease

Y. Hu (✉) • S. Pan
Department of Neurology, Nanfang Hospital, Southern Medical University, 1838 North Guangzhou Avenue, Guangzhou, Guangdong 510515, China
e-mail: yafanghu@smu.edu.cn; pansuyue82@126.com

H.-T. Zhang
Department of Behavioral Medicine and Psychiatry, West Virginia University Health Sciences Center, 1 Medical Center Drive, Morgantown, WV 26506, USA

Department of Physiology and Pharmacology, West Virginia University Health Sciences Center, 1 Medical Center Drive, Morgantown, WV 26506, USA

Institute of Pharmacology, Taishan Medical University, Taian, 271016 China
e-mail: hzhang@hsc.wvu.edu

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conditions. Their specific relationship and interaction, however, remains to be elucidated. In this review, we summarize the phosphorylation of the elements in the cAMP signaling pathway by both Cdk5 and cAMP/PKA. In addition, we highlight the Cdk5 regulation of phosphodesterase-4 (PDE4), a critical regulator of intracellular cAMP levels, in memory and learning and responses to stress exposure.

3.2 Cdk5 and Cdk5 Cofactors

Cdk5 belongs to the Cdk family of serine/threonine kinases (Lew et al. 1992; Meyerson et al. 1992). Unlike most Cdks, Cdk5 is activated by one of two noncyclin cofactors, p35 (Tsai et al. 1994) and p39 (Tang et al. 1995). Cdk5 is ubiquitously expressed in all cells and tissues, while p35 is highly expressed in embryonic neurons and p39 prominently in synapses of the postnatal brain (Humbert et al. 2000) and oligodendroglia (Bankston et al. 2013). Accordingly, the highest activity of Cdk5 is identified in the brain (Su and Tsai 2011). Mice deficient in Cdk5 ($Cdk5^{-/-}$) display perinatal lethality associated with abnormal corticogenesis and cerebellar defoliation due to neuronal migration deficits and impaired axonal transport of neurofilaments (Ohshima et al. 1996). Notably, $p35^{-/-}$ animals exhibit less severe cortical lamination defects compared to Cdk5 null mice and suffer from sporadic adult lethality and seizures (Chae et al. 1997). Mice with p39 deficiency do not result in overt detrimental phenotypes, (Ko et al. 2001) but exhibit impaired remyelination (Bankston et al. 2013). However, p35 and p39 double knockout mice exhibit nearly identical phenotypes to Cdk5-null mice (Ko et al. 2001). Thus, Cdk5/p35 appears to play a major role in neurons, (Su and Tsai 2011) whereas Cdk5/p39 may be critical for oligodendroglia differentiation (Bankston et al. 2013).

p35 is prominently located in perimembrane due to its N-terminal myristoylated region. It is rapidly degraded by the proteasome. Under neurotoxic conditions, p35 is converted into N-terminal p10 and C-terminal p25 fragments. p25 is characterized by predominant cytoplasm and nucleus location and retains the Cdk5 binding site. Compared to p35, p25 is more resistant to proteasome degradation and has fivefold longer half-life and, consequently, extends Cdk5 activity (Patrick et al. 1999). More than sixty Cdk5 substrates have been identified (Su and Tsai 2011). By targeting on a myriad of downstream substrates, Cdk5/p35 play an essential role in brain development, neuronal survival, synaptic plasticity, learning and memory formation, (Su and Tsai 2011; Dhavan and Tsai 2001) whereas Cdk5/p25 have been considered to be involved in neurotoxicity and neurodegeneration (Patrick et al. 1999; Cruz et al. 2003; Nguyen et al. 2001). With mislocation, p25, unlike p35, may target not only physiological substrates, but also disease-associated substrates (Lew 2013).

3.3 Cdk5 Phosphorylates Multiple Substrates of the cAMP Signaling Pathway

cAMP, together with cGMP, are two important second messengers that mediate numerous CNS functions, including cell signaling, synaptic transmission, neuronal survival, neuron development, and cognition. The levels of both cAMP and cGMP are tightly controlled to maintain the specificity and integrity of the intracellular signal propagation (Hebb and Robertson 2007). cAMP synthesis is catalyzed by adenylyl cyclase (AC), and breakdown is carried out by the enzyme PDE4. cAMP activates PKA, which phosphorylates the transcription factor cAMP-response element binding protein (CREB) and PDE4 at Ser 133; the latter forms a negative feedback loop. Cdk5 modulates cAMP/PKA signaling at multiple steps by directly phosphorylating several downstream substrates, including PDE4, dopamine- and cAMP-regulated phosphoprotein, Mr 32 kDa (DARPP-32), protein phosphatase 1 (PP1), and tyrosine hydroxylase (TH), which are summarized at the end of section 3.3.

3.3.1 PDE4

PDE4 has four subtypes (PDE4A-D), which are encoded by four distinct genes, consisting of at least 25 splice variants (Li et al. 2011). Their differential distributions in the brain indicate different roles of individual PDE4 subtypes in CNS functions (Perez-Torres et al. 2000). With the exception of PDE4C, which is primarily expressed in peripheral tissues and has limited expression in the human brain (cortex, thalamic nuclei, and cerebellum), all other PDE4 subtypes (PDE4A, B, and D) are widely and differentially distributed in the brain (Perez-Torres et al. 2000). Specifically, PDE4A and PDE4D are the major subtypes expressed in the hippocampus, while PDE4B is prominent in the striatum, including the nucleus accumbens (NAc). Functionally, PDE4A is involved in anxiety (Hansen et al. 2014); PDE4B is associated with schizophrenia (Millar et al. 2005; Liu et al. 2016), anxiety (Zhang et al. 2008), and depression (Plattner et al. 2015); and PDE4D is important for antidepressant activity (Zhang et al. 2002), memory (Giorgi et al. 2004), and synaptic plasticity (Rutten et al. 2008). Long-form PDE4s which containing the upstream conserved regions (UCR1 and UCR2) in the N-terminus are most important in cAMP hydrolysis (Baillie et al. 2000). It has been found that Cdk5 efficiently phosphorylates PDE4B1 at Ser145 located in the UCR1 domain and results in activation of PDE4 (Plattner et al. 2015). The Cdk5 site (Ser 145) and PKA site (Ser 133), which is also located in the UCR1 domain, synergistically activate PDE4 (Plattner et al. 2015). Since UCR1 is conserved in all long PDE4s, whether Cdk5 can phosphorylate all long-form PDE4 isoforms remains to be determined.

3.3.2 DARPP-32 and PP1

DARPP-32, a postsynaptic protein highly expressed in striatal medium-size spiny neurons, was identified initially as a major target for dopamine in the striatum. Dopamine binding to D1 receptors increases cAMP and subsequently activates PKA, which phosphorylates DARPP-32 at Thr34 and converts it into a potent inhibitor of PP-1 (Hemmings et al. 1984). PP-1 is a Ser/Thr phosphatase which controls the phosphorylation status and activity of a variety of downstream effector molecules including CREB. Cdk5 phosphorylates DARPP-32 at Thr75, which in turn inhibits PKA (Bibb et al. 1999). In other words, DARPP-32 acts as an inhibitor of either PP-1 by PKA phosphorylation or PKA by Cdk5 phosphorylation. In cortical neurons, Cdk5 phosphorylates PP1 at T320 which suppresses PP1 activity. Under synaptic N-methyl-D-aspartate (NMDA) receptor stimulation, p35 degradation leads to a loss of Cdk5 activity and activation of PP1 (Hou et al. 2013). The complex network of positive and negative feedback is indicated as in Fig. 3.1.

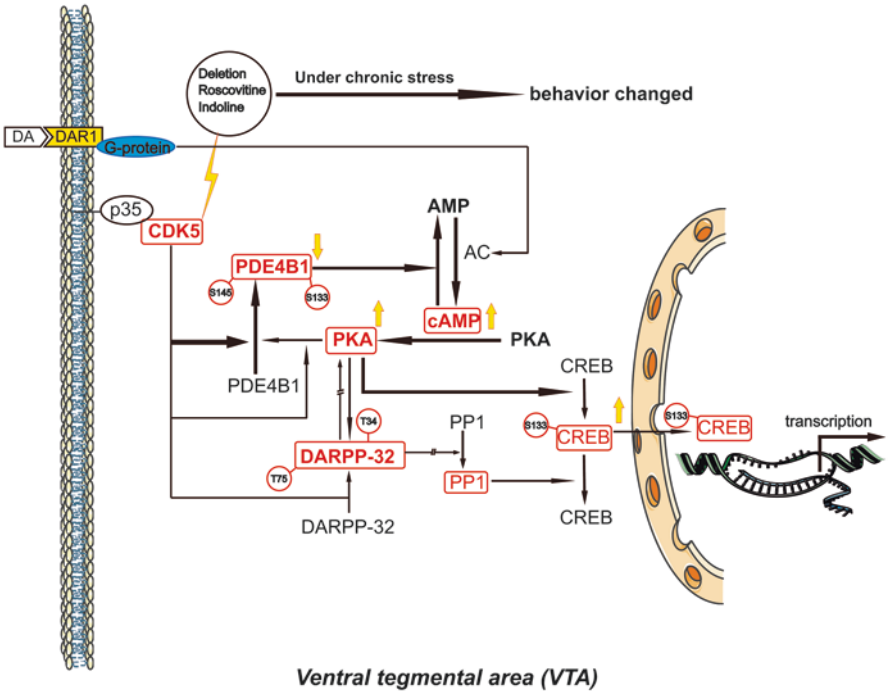

Fig. 3.1 Cdk5 negatively regulates PDE4 signaling in the VTA of the striatum. *Red* fond representing phosphorylated protein with the phosphorylated site labeled. *Arrows* indicate improving, *blocked arrows* indicate inhibiting. *T* Thr, *S* Ser

3.3.3 TH

TH is the rate-limiting enzyme for dopamine synthesis in presynaptic terminals. When phosphorylated, it has an increased activity. This can be accomplished by several kinases, including PKA at Ser 40 and Ca^{2+}-calmodulin-dependent protein kinase II (CaMKII) at Ser19 (Haycock et al. 1998). Cdk5 also plays a critical role in the regulation of TH activity; it phosphorylates TH at Ser 31 (Moy and Tsai 2004). In addition, transgenic mice with increased Cdk5 activity display increased TH Ser 31 phosphorylation in neurons of the substantia nigra, which is enriched with TH-positive neurons (Moy and Tsai 2004). On the other hand, Cdk5 deficiency reduces TH levels. TH is also phosphorylated at the same site by extracellular signal-regulated kinases 1/2 (ERK1/2) (Moy and Tsai 2004). Cdk5 phosphorylation at Ser 31 modulates ERK1/2-dependent phosphorylation of TH through the phosphorylation of mitogen-activated protein kinase 1 (MEK1), providing another route by which Ckd5 regulates TH activity (Kansy et al. 2004).

3.3.4 Coronin 1

Coronin 1 belongs to the family containing WD repeat, which is a structural motif comprising approximately 40 amino acids usually ending with the amino acid sequence tryptophan (W) and aspartic acid (D). It is expressed in leukocytes and neurons, particularly in excitatory neurons (Ferrari et al. 1999). Increase copy numbers in the genomic region of coronin 1 located in chromosome 16 causes varying degrees of cognitive impairment (Horev et al. 2011). Upon cell surface stimulation, coronin 1 assembles with the G protein subunit Gαs to increase cAMP production. Being an upstream modulator, Cdk5 can phosphorylate coronin 1 in T lymphocytes (Pareek et al. 2010). In human melanoma cells (Mel JuSo), Cdk5 phosphorylates coronin 1 at Thr 418 and 424. The Cdk5-dependent phosphorylation of coronin 1 is essential but not sufficient for Gαs-mediated cAMP production, suggesting additional mechanisms upstream of coronin 1 to activate the coronin 1-dependent cAMP/PKA pathway (Liu et al. 2016).

3.3.5 Disrupted-in-Schizophrenia 1 (DISC1)

The Disrupted-in-Schizophrenia 1 (DISC1) is a susceptibility factor for multiple mental disorders, including schizophrenia, mood disorders, and autism. It is expressed in both neuronal progenitor cells and postmitotic neurons in the developing cerebral cortex (Ishizuka et al. 2011). DISC1 can be phosphorylated at two sites, Ser58 and Ser710, by PKA and Cdk5, respectively. Cdk5-mediated phosphorylation

of DISC1 at Ser710 acts as a molecular switch from maintaining proliferation of mitotic progenitor cells to activating migration of postmitotic neurons (Kamiya et al. 2008). The function of phosphorylation of Ser58 by PKA is unclear.

3.3.6 Synapsin III

Synapsin III (SynIII) is an atypical member of the synapsin family of neuron-specific phosphoproteins associated with synaptic vesicles (SVs). Among the three Synapsins (I, II, III), SynIII is the earliest expressed Syn isoform during development (Porton et al. 1999; Porton et al. 2004). In addition to a highly conserved phosphorylation site (Ser 9) for PKA shared by all Syn isoforms, SynIII has a specific domain J containing a phosphorylation site for Cdk5 at Ser404 (Perlini et al. 2015; Piccini et al. 2015). Cdk5 and SynIII expression are highly correlated at perinatal ages in rat cortical neurons. SynIII acts on downstream Sema3A/Cdk5 signaling to play an important role in neuronal migration and orientation (Perlini et al. 2015; Ferreira et al. 2000). It has been found that phosphorylation of SynIII at Ser9 by PKA and Ser404 by Cdk5 are equally important at the early neuronal development (Piccini et al. 2015). Colectively, the downstream substrates of cAMP/PKA signaling pathwy contain phosphorylation sites of Cdk5 and PKA, summarized as in Table 3.1.

3.4 Cdk5 Is Associated with Memory, Learning via the cAMP Signaling Pathway

The hippocampus is considered to be a key region for long-term memory formation in humans and rodents (Morris et al. 1982). Memory formation is modulated by pre- and post-synaptic signaling events in neurons which affect synaptic plasticity. Synaptic plasticity can produce decreases or increases in the amplitude of synaptic responses, called depression or potentiation, respectively.

Table 3.1 The phosphorylation sites of downstream substrates by Cdk5 or PKA

Substrates	Cdk5 sites	PKA sites
PDE4	Ser 145	Ser 133
DARPP-32	Thr 75	Thr 34
PP1	Thr 320	
TH	Ser 31	Ser 40
Cornin1	Thr418, Thr 424	Upstream of PKA
DSCI1	Ser 710	Ser 58
SnyIII	Ser 404	Ser 9

Activation of cAMP/PKA signaling enhances synaptic plasticity through phosphorylation of its downstream target CREB, which activate related genes expression (Bruel-Jungerman et al. 2005). Consistent with this, PDE4 is involved in hippocampal neurogenesis, which is associated with learning and memory (Egawa et al. 1997). Chronic rolipram treatment to specifically inhibit PDE4 increases proliferation and survival of newborn neurons in the hippocampal dentate gyrus (Nakagawa et al. 2002; Sasaki et al. 2007). Inhibition of PDE4 also enhances memory or reverses memory deficits produced by pharmacological, (Egawa et al. 1997; Zhang et al. 2000; Zhang et al. 2004) physical, or genetic approaches (Sierksma et al. 2014; Imanishi et al. 1997; Bourtchouladze et al. 2003). Similar results are observed in PDE4D-deficient mice, which showed increased hippocampal neurogenesis and phosphorylated CREB in the brain. miRNA-mediated PDE4D knockdown in the hippocampus demonstrates that PDE4D, in particular long-form PDE4Ds, plays a critical role in the mediation of memory and hippocampal neurogenesis (Li et al. 2011; Zhang et al. 2014; Wang et al. 2013; Wang et al. 2015). These are consistent with the findings using pharmacological approaches (Sierksma et al. 2014; Bruno et al. 2011).

Cdk5 is also implicated in memory formation by phosphorylating a variety of synaptic substrates. The first hint suggesting a role of Cdk5 in hippocampus-dependent memory formation came from a study with p35 knockout (KO) mice, which displayed normal LTP, but impaired LTD in the CA1 subregions of the hippocampus (Ohshima et al. 2005). Another hint was from p25 transgenic (Tg) mice showing that p25 appeared to have dual effects in synaptic plasticity. Adult CK-p25 Tg mice with p25 overexpressed for 2 weeks, which is driven by the CaMKII promoter and turned on by aTA system, displayed dramatic enhancement of learning and memory in contextual fear conditioning and the Morris water-maze tasks (Fischer et al. 2005). This memory-enhancing effect is consistent with facilitation of LTP and increases in dendritic spines in hippocampal CA1. However, long-term, 6-week induction of p25 resulted in severe neuronal loss, memory impairment, and LTP deficit.

Additional findings associating Cdk5 activity with memory seem controversial. In an inducible Cdk5 conditional knockout (cKO) line, which was derived under a prion promoter (Hawasli et al. 2007), the Cdk5 cKO mice display facilitated LTP and enhanced memory via reduced degradation of the NR2B subunit of NMDA receptors. In contrast, a different line of Cdk5 cKO mice, whose Cdk5 is ablated primarily in CA1 pyramidal neurons of the hippocampus at early age (2.5–3.5 months old), exhibited severe impairment in hippocampus-dependent spatial memory. Memory impairment was also observed in Cdk5 cKO mice with forebrain-targeted Cdk5 deletion in excitatory neurons (Fischer et al. 2005).

In Cdk5f/f/T29 cKO mice in which Cdk5 ablation is restricted mainly to CA1 pyramidal neurons of the hippocampus, it has been demonstrated that Cdk5 mediates synaptic plasticity and hippocampus-dependent memory via modulation of cAMP signaling (Guan et al. 2011). In the Cdk5 KO mice, increased mRNA levels of multiple PDE isoforms, including PDE4B, PDE4D, PDE4D4, PDE1A, and PDE2A, were observed in the hippocampus. Low cAMP causes insufficient CREB

phosphorylation at Ser 133, leading to decreases in synaptic proteins and impairment of learning and memory. Treatment with the PDE4 inhibitor rolipram rescues the behavioral deficits in Cdk5 cKO mice.

The Cdk5 mediation of memory via cAMP/PKA is supported by a recent finding that Cdk5 regulates coronin 1-dependent cAMP/PKA signaling (Liu et al. 2016). Coronin 1, the upstream trigger of cAMP/PKA signaling, has been found to regulate cAMP production and PKA activation (Jayachandran et al. 2014). Coronin 1 deficiency results in severe functional defects at excitatory synapses. Furthermore, in both mice and humans, deletion or mutation of coronin 1 causes severe neurobehavioral defects, including social deficits, increased aggression, and learning disabilities. Infusions of the cAMP analogue 8-Br-cAMP into the amygdala restore synaptic plasticity and behavioral defects in mice lacking coronin 1. It is interesting to note that Cdk5 is able to phosphorylate coronin 1 on Thr 418 and 424 in cultured neurons. This provides evidence that Cdk5 regulates the coronin 1-dependent cAMP/PKA signaling pathway, even if Cdk5-dependent phosphorylation of coronin 1 is not sufficient for Gαs-mediated cAMP production (Liu et al. 2016). It will be important to check this pathway in extended studies with animal models.

Together, both cAMP/PKA signaling and Cdk5 are involved in the mediation of learning and memory. Cdk5 regulates cAMP/PKA signaling via phosphorylation of the elements upstream and downstream of the pathway.

3.5 Cdk5 Regulates PDE4 Signaling on Stress Exposure and Its Association with Anxiety and Depression

Under acute and chronic stress procedures, several brain areas are important for neurobiological responses to stress exposure, including the amygdala and the ventral tegmental area (VTA). The limbic system controls emotional behavior and motivational drives. The amygdala, in particular the basolateral amygdala (BLA), modulates negative emotional reactions to threatening environment. Dopamine neurons in the VTA govern reward and motivation and mediate stress-induced behaviors (Chaudhury et al. 2013; Tye et al. 2013).

The activity of both Cdk5 and p35 is increased in various brain areas of the limbic system in response to stress stimulation. Stress exposure increases p35 levels particularly in the BLA, which is correlated with the occurrence of exaggerated anxiety. This is selectively reversed by infusions of olomoucine, a Cdk5 inhibitor, into the BLA, but not the adjacent CeA, prior to the restraint session, suggesting a role of Cdk5 (Bignante et al. 2010; Bignante et al. 2008). In a p25 transgenic (p25-Tg) mouse model created using the neuron-specific enolase promoter that expresses human p25 cDNA, (Ahlijanian et al. 2000) it has been demonstrated that upregulation of p25 increases locomotor activity and decreases anxiety-like behavior. These results suggest a pivotal role of the Cdk5/p35 complex in excessive anxiety induced by a previously stressful experience.

Early studies suggest a reciprocal, regulatory relationship between PKA and Cdk5 activity (Bibb et al. 1999). Infusions of a Cdk5 inhibitor into the hippocampal dentate gyrus (DG), but not CA1 or CA3, increase sucrose preference and prevent locomotor impairment in response to chronic mild stress, supporting antidepressant activity (Zhu et al. 2012). Since selective increases in cAMP levels in VTA dopamine neurons reverse behavioral deficits induced by Cdk5 deletion, the results imply that Cdk5 may regulate cAMP/PKA signaling upstream. This hypothesis has been demonstrated by a recent study showing that Cdk5 directly potentiates PDE4B1 activity via phosphorylation, causing downregulation of cAMP levels in striatal slices (Plattner et al. 2015). Inhibition of Cdk5 by roscovitine increases phosphorylation of cAMP/PKA downstream substrates in striatal slices, including CREB (Ser133) and DARPP-32 (Thr34). This observation was further confirmed in an AAV2-mediated mouse model, in which medium spiny neurons in the ventral striatum and D1 dopamine receptor positive neurons were specifically targeted. Consistent with these results, virus-mediated Cdk5 KO in the ventral striatum and D1R-Cdk5-KO mice all showed consistent biochemical and behavioral effects suggesting antidepressant-like effects (e.g. reduced immobility time in Porsolt forced-swim test, increased time struggling in tail suspension test and social interaction ratio in social defeat stress, and elevated sucrose preference). In addition, specific disruption of Cdk5 in the VTA or dopamine neurons by VTA infusions of adeno-associated viral-Cre in Cdk5loxP/loxP mice or breading dopamine transporter (DAT)-Cre mice with Cdk5loxP/loxP mice decreases dopamine-release in the ventral striatum, reduces motor activity in response to acute stress, prolongs novel environment-related feeding delay, and reduces sucrose preference, which paradoxically suggest anxiety- and depressive-like behaviors (Zhong et al. 2014). These mice also show decreases in TH phosphorylation at Ser31 (Cdk5 site) and Ser40 (PKA site), cAMP, and phosphorylated CREB (ser133) in the VTA. The reason for the contradictory observations remains to be clarified, while brain region-specific responses to Cdk5 disruption cannot be excluded.

Overall, in the VTA of the striatum, Cdk5 provides a negative feedback on cAMP/PKA signaling by potentiating PDE4 activity via phosphorylation. Deletion of Cdk5 in the VTA increases cAMP levels and PKA activity, thereby affecting behavioral responses induced by acute and chronic stress, as indicated in Fig. 3.1. Nevertheless, it remains to be resolved how biological responses cause the behavioral changes.

3.6 Reciprocal Regulation of Cdk5 and cAMP/PKA Signaling on Dopaminergic Signaling and Its Association with Parkinson's Disease

Striatal functions depend on an activity balance between dopamine and glutamate transmissions that produce opposing physiological effects (Greengard 2001; Chergui et al. 2004). Dopamine inputs activate PKA, thus phosphorylating

DARPP-32 at Thr 34, which inhibits PP1, the enzyme responsible for dephosphorylation of Ser-133 of CREB (Hemmings et al. 1984). Glutamate inputs activate Cdk5, thus phosphorylating DARPP-32 at Thr75, which functions as an inhibitor of PKA. Therefore, DARPP-32 plays as an integrator to balance dopamine and glutamate transmissions (Svenningsson et al. 2004; Fernandez et al. 2006; Bonito-Oliva et al. 2011). It is noted that under resting conditions, DARPP-32 is highly phosphorylated at Thr 75 and slightly phosphorylated at Thr34 (Greengard 2001; Sako et al. 2010). Upon stimulation or under disease conditions, the homeostasis of this balance is disrupted. Dysregulation of Cdk5 activity has been implicated in striatal dopamine-related disorders such as Parkinson's disease (PD) (Chergui et al. 2004; Smith et al. 2003; Qu et al. 2007) and drug addiction (Takahashi et al. 2005; Bibb et al. 2001).

In a rodent model of PD, striatal dopamine deficiency had no effect on phosphorylation of Thr34-DARPP-32, but significantly increased that of Thr75-DARPP-32 (Brown et al. 2005). In MPTP mice, dopamine deficiency increased Cdk5-pTyr15 and Thr75-DARPP-32 via the D2R pathway. In addition, calpain caused aberrant formation of p25 and accompanied Cdk5 hyperactivity in MPTP mice (Qu et al. 2007; Huang et al. 2010; Smith et al. 2006). Since activation of Cdk5 also phosphorylates PDE4 as it does in VTA, it is possible that aberrant Cdk5 activity may increase PDE4 phosphorylation and inhibit PKA activity, and thus worsen DA neuron loss.

3.7 Interaction of Cdk5 and cAMP/PKA Pathway in Dopamine Signaling and Its Association with Drug Addiction

Cocaine, a drug of abuse, increases synaptic dopamine levels in the striatum by blocking dopamine reuptake at axon terminals. Acute cocaine inhibits dopamine synthesis in a dose-dependent manner via a putative negative feedback mechanism.

Chronic cocaine exposure increases ΔFosB, a Fos family transcriptional factor in the striatum, resulting in the elevation of Cdk5 and p35 in medium spiny striatal neurons (Bibb et al. 2001). Cdk5 activation increases phosphorylation of DARPP-32 at Thr75 and subsequently attenuates D1R/PKA signaling. This is supported by the observation in DARPP-32 mutant mice (Hiroi et al. 1999). Cdk5 activation also phosphorylates TH at Ser31 in dopaminergic neurons of rats trained to chronically self-administer cocaine (Lu et al. 2003). Inhibition of Cdk5 in the striatum has been shown to potentiate behavioral effects of chronic cocaine treatment in animals (Taylor et al. 2007). In a p35 transgenic mouse line, overexpression of p35 decreases cocaine-induced phosphorylation of CREB (at Ser133) and that of MEK1/2 (at Ser217/Ser221 or Thr202/Tyr204), and DARPP-32 (at Thr34), but increases cocaine-induced phosphorylation of DARPP-32 (at Thr75) and MEK1/2 (at Thr286) (Ohshima et al. 1996). The results provide further evidence that Cdk5 mediates

cocaine-induced dopamine signaling through inhibition of the PKA and ERK cascades, leading to less induction of CREB phosphorylation and c-fos in the striatum.

Methamphetamine (METH), another illicit substance of abuse, acts as a substrate for the dopamine transporter and the vesicular monoamine transporter and causes intense psychomotor activating and motivational properties (Bosse et al. 2015). Repeated use of METH leads to behavioral sensitization and addition. The cAMP/PKA pathway implicates in conferring METH-induced synaptic modifications in striatal reward neurocircuits (Bosse et al. 2015; Moriguchi et al. 2002; Miyazaki et al. 2013). For example, a recent study demonstrates a blunted, acute and sensitized locomotor response to METH in mice with AC1 and AC8 double knockout (DKO) (Bosse et al. 2015). Compared to WT controls, DKO mice displayed significantly low levels of dopamine and decreases in the ratio of phosphorylation of DARPP-32 at Thr-34 (the PKA site) relative to Thr-75 (the Cdk5 site) after repeated exposure to METH. This study suggest that AC modulates interaction between Cdk5 and cAMP/PKA pathway in drug addiction.

3.8 Role of Cdk5 and cAMP/PKA Signaling in Mediating Neuropsychiatric Disorders

The DISC1 gene is a generalized risk factor in major mental illnesses, including bipolar disorder, major depression, and schizophrenia (Blackwood et al. 2001; Millar et al. 2000; Hennah et al. 2007; Porteous and Millar 2006). Disruption of PDE4B due to a balanced translocation is also identified as a genetic risk factor for psychiatric illnesses such as schizophrenia, (Hansen et al. 2014) which is supported by the association of PDE4B polymorphisms with schizophrenia (Guan et al. 2012). The interaction between DISC1 and several other proteins, including PDE4B, NDEL1, FEZ1, and GSK3β, is involved in the molecular mechanism of schizophrenia. In addition, phosphorylation of DISC1 at Ser710 by Cdk5 triggers the recruitment of Bardet-Biedl-Syndrome (BBS) proteins to the centrosome, which underlie neuronal migration (Kamiya et al. 2008). It is speculated that disturbance of this switch mechanism may contribute to hypertrophic and disturbed corticogenesis observed in brains of patients with autism.

Several reports suggest an association of SynIII with neurodevelopmental disorders such as schizophrenia by analysis of postmortem samples (Porton and Wetsel 2007) or genetic studies (Porton et al. 2004; Chen et al. 2009). Synapsins play a primary role in synaptic transmission and plasticity (Valtorta et al. 1992; Cesca et al. 2010; Fornasiero et al. 2012). In addition, Syns also play a critical role in neuronal development by regulating neurite outgrowth and synapse formation (Fornasiero et al. 2010; Perlini et al. 2011). SynIII is the isoform expressed earliest in neurons compared to Syn I and II. Structurally, SynIII contains a major Cdk5 phosphorylation site (Ser404) in the unique domain J, while all three Syns share a

highly conserved PKA phosphorylation site (Kao et al. 1999). Phosphorylation of SynI by PKA modulates synapse formation in vitro (Perlini et al. 2011), and phosphorylation of SynII by PKA plays a crucial role in Xenopus spinal neurons. Phosphorylation of SynIII by Cdk5 in vivo regulates the radial migration of pyramidal neurons in cortical development (Perlini et al. 2015). SynIII KO in embryonic neurons impairs inhibitory transmission, but the phenotype is mild (Feng et al. 2002). Furthermore, phosphorylation of SynIII by PKA and Cdk5 are both required at the early neuronal development, because the Cdk5 or PKA phospho-mimetic mutation of SynIII only partially rescues the developmental phenotype of SynIII KO (Piccini et al. 2015).

Taken together, both Cdk5 and cAMP/PKA signaling pathways are involved in DISC1- and SnyIII-mediated mental illnesses including schizophrenia. Determination of whether these two pathways are independent or in crosstalk will help us better understand the mechanisms underlying the development of the psychiatric diseases, which could lead to novel therapeutic strategies.

3.9 Conclusions

Accumulating evidences support significant interactions between Cdk5 and cAMP/PKA signaling, which play an important role in multiple important functions of the CNS, including cognition, drug addiction, and mental behaviors. Cdk5 regulates cAMP signaling via phosphorylation of its upstream and/or downstream components, including PDE4B, DARPP-32, ERK, and CREB. PKA in turn also regulates Cdk5 activity via phosphorylation of DARPP-32 at a different phosphorylation site. It should be noted that other critical players not summarized here such as anchoring proteins also serve as mediators to integrate the activity of Cdk5 and PKA in neuronal environment. Primarily through these mechanisms, Cdk5 is involved in the mediation of a variety of CNS disorders, including AD, PD, depression, anxiety, schizophrenia, and drug addiction, in which Cdk5 is in hyperphosphorylation and/or dysfunction. More studies are needed to understand the related cellular and molecular mechanisms underlying neuropsychiatric and neurodegenerative diseases, which could aid in the development of novel treatments of these diseases.

Conflict of Interest The authors declare that they have no conflicts of interest.

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