Neuron 50, 13–18, April 6, 2006 ©2006 Elsevier Inc. DOI 10.1016/j.neuron.2006.02.024

Synaptic Roles of Cdk5: Implications in Higher Cognitive Functions and Neurodegenerative Diseases

Minireview

Zelda H. Cheung,[1] Amy K.Y. Fu,[1] and Nancy Y. Ip[1,*]
[1] Department of Biochemistry
Biotechnology Research Institute and
Molecular Neuroscience Center
Hong Kong University of Science and Technology
Hong Kong
China

Accumulating evidence indicates that cyclin dependent kinase 5 (Cdk5), through phosphorylating a plethora of pre- and postsynaptic proteins, functions as an essential modulator of synaptic transmission. Recent advances in the field of Cdk5 research have not only consolidated the in vivo importance of Cdk5 in neurotransmission but also suggest a pivotal role of Cdk5 in the regulation of higher cognitive functions and neurodegenerative diseases. In this review, we will discuss the recent findings on the emanating role of Cdk5 as a regulator of synaptic functions and plasticity.

Cdk5, a proline-directed serine/threonine kinase, is a unique Cdk that is activated by two noncyclin activators, p35 and p39. As a predominantly neural-specific kinase, Cdk5 lacks a role in cell-cycle control but is implicated in an astounding array of neuronal functions, including neuronal survival, axon guidance and neuronal migration. The ever expanding list of Cdk5 substrates as well as the functions modulated by Cdk5 have recently been reviewed elsewhere (Cheung and Ip, 2004; Cruz and Tsai, 2004; Dhavan and Tsai, 2001) and, hence, will not be the focus of the current review. Among the various biological functions implicated, the emerging role of Cdk5 as a regulator of neurotransmission and synaptic plasticity has attracted increasing attention (Cheng and Ip, 2003). Indeed, a myriad of pre- and postsynaptic proteins have been identified as Cdk5 substrates. More importantly, accumulating evidence has lent support for an in vivo role of Cdk5 in the regulation of neurotransmission and synaptic functions in learning and neurodegenerative diseases. In this review, we summarize the latest evidence on the pre- and postsynaptic roles of Cdk5 and the involvement of this kinase in higher cognitive functions and neurodegenerative diseases such as Alzheimer's disease.

Presynaptic Roles of Cdk5

Neurotransmitter release is tightly regulated through the precise control of the synaptic vesicle cycle, which is comprised of Ca^{2+}-triggered exocytosis of synaptic vesicles, followed by retrieval and recycling of synaptic vesicles via clathrin-mediated endocytosis, and finally clathrin uncoating of synaptic vesicles. Through the phosphorylation of synapsin I, Munc18, and P/Q subtype voltage-dependent calcium channel (VDCC), Cdk5 has been associated with regulating the exocytosis episode of the synaptic vesicle cycles (reviewed in Cheng and Ip [2003]). Interestingly, a Cdk-related kinase Pctaire1, whose activation in vivo is attributable at least in part to Cdk5-mediated phosphorylation (Cheng and Ip, 2003), may also play a role in regulating exocytosis. Pctaire1 can phosphorylate NSF, a crucial factor for synaptic vesicle fusion, and thereby suppress NSF oligomerization, a step essential for exocytosis (Liu et al., 2006). This observation indicates that Cdk5-mediated activation of Pctaire1 may hinder exocytosis by suppressing oligomerization of NSF, thus revealing a novel mechanism by which Cdk5 may regulate exocytosis.

In addition to the regulation of exocytosis, Cdk5 was also identified as a kinase for dynamin I and amphiphysin I, proteins essential for clathrin-mediated endocytosis (Tan et al., 2003; Tomizawa et al., 2003). Recent studies have extended the importance of Cdk5 in synaptic vesicle endocytosis through demonstrating a novel role of Cdk5 in the modulation of phosphoinositides (PIs) signaling pathways. $PI(4,5)P_2$ has been implicated in the plasma membrane recruitment of proteins involved in synaptic vesicle endocytosis, thus underscoring the importance of regulating $PI(4,5)P_2$ levels and localization in the execution of synaptic vesicle endocytosis. Interestingly, PIPKIγ, the kinase involved in the generation of $PI(4,5)P_2$, and synaptojanin 1, a $PI(4,5)P_2$ phosphatase, were both recently identified as substrates of Cdk5 (Lee et al., 2004, 2005). Phosphorylation of PIPKIγ by Cdk5 disrupts its association with focal adhesion protein talin (Lee et al., 2005), an interaction that is essential for clathrin-mediated synaptic vesicle endocytosis (Morgan et al., 2004). Additionally, Cdk5-mediated phosphorylation of synaptojanin 1 inhibits its phosphatase activity and recruitment to the membrane. In accordance with the implication of synaptojanin 1 in clathrin uncoating of synaptic vesicles, inhibition of synaptojanin 1 activity by Cdk5 suppresses this process (Lee et al., 2004). Collectively, these findings indicate that Cdk5 may potentially function as a negative regulator of neurotransmitter release. In support of this notion, Cdk5 has been implicated in the inhibition of dopamine release in the striatum (Chergui et al., 2004). Furthermore, the frequency of miniature endplate potential (MEPP) is increased in $Cdk5^{-/-}$ mice (Fu et al., 2005), thus supporting an inhibitory role of Cdk5 in neurotransmitter release in vivo.

Postsynaptic Roles of Cdk5

Regulation of Neurotransmitter Receptor Expression

An unexpected functional role of Cdk5 at the synapse was initially revealed through the identification of Cdk5 as a crucial mediator of neuregulin (NRG) signaling and AChRε expression in myotubes (Fu et al., 2001). Cdk5-mediated phosphorylation of NRG receptor ErbB3 is required for NRG-induced ErbB3 activation, initiation of downstream signaling, and enhancement in AChRε transcription in myotubes. A recent study revealed that NRG-mediated transcription of neurotransmitter receptor is similarly observed in cultured cerebellar granule neurons. NRG-induced activation of ErbB4 results in Cdk5-dependent upregulation of $GABA_A$ receptors

*Correspondence: boip@ust.hk

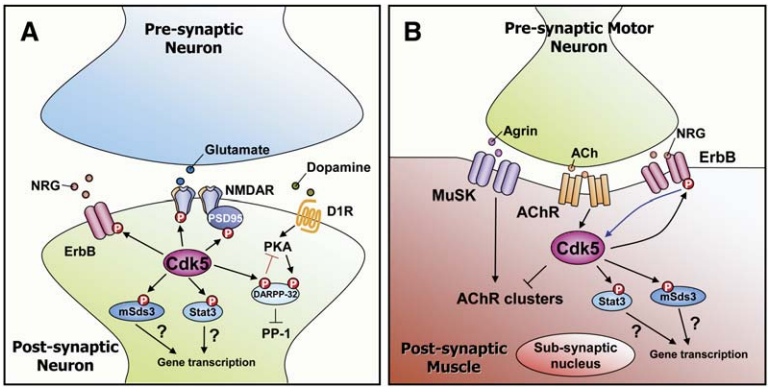

Figure 1. Postsynaptic Role of Cdk5 on the Regulation of Synaptic Transmission

Cdk5 affects neurotransmitter receptors expression and clustering at both the CNS synapse (A) and the NMJ (B). (A) At the CNS synapse, NRG-mediated transcription of neurotransmitter receptor such as $GABA_A$ receptors requires Cdk5 activity. Nonetheless, whether this is attributable to the demonstrated phosphorylation of ErbB receptors by Cdk5 in the CNS requires further investigation. On the other hand, Cdk5 may also regulate gene transcription by phosphorylating transcription factor STAT3 or by regulating histone acetylation through phosphorylation of HDAC corepressor complex component mSds3. Furthermore, while Cdk5 suppresses multimerization of PSD-95 and clustering of NMDA receptors via the phosphorylation of scaffold protein PSD-95, Cdk5-mediated phosphorylation of NMDA receptors enhances NMDA-evoked current and LTP induction. Finally, Cdk5 also dampens dopamine signaling through phosphorylation of DARPP-32 at Thr 75, turning DARPP-32 into an inhibitor of PKA to reduce phosphorylation of DARPP-32 at Thr 34 and initiation of downstream signaling. (B) At the NMJ, NRG stimulation induces Cdk5 activity, which in turn affects AChR transcription by regulating ErbB signaling in the myotubes, although the precise mechanisms by which AChR transcription is regulated in vivo remain elusive. On the other hand, Cdk5 may regulate gene transcription via phosphorylation of STAT3 or phosphorylation of HDAC corepressor complex component mSds3. Finally, although agrin-induced MuSK activation provides essential signals for maintenance of AChR clusters, recent evidence suggests that Cdk5 also modulates AChR clustering by facilitating AChR dispersal, with ACh stimulation being one of the upstream AChR dispersing signals.

transcription in these CNS neurons (Xie et al., 2004) (Figure 1). Because Cdk5 has been observed to phosphorylate ErbB2/3 in the brain (Cheung and Ip, 2004), it would be of interest to examine if Cdk5 mediates NRG-induced increase in $GABA_A$ receptor transcription through the phosphorylation of ErbB4 in cerebellar granule neurons.

The mechanisms by which Cdk5 mediates NRG-induced transcription of neurotransmitter receptor are barely beginning to be unraveled. However, recent observations have provided some clues. Cdk5 may mediate NRG-induced gene transcription in myotubes through the regulation of transcription factor STAT3. NRG treatment results in an increase in Cdk5-mediated serine phosphorylation of STAT3, which enhances STAT3 DNA binding activity and subsequent transcription of c-*fos*. Importantly, serine phosphorylation of STAT3 is essentially abolished in $Cdk5^{-/-}$ brain and muscle, indicating that Cdk5 is a critical regulator of this event in vivo (Fu et al., 2004). Nonetheless, with the recent observation on the lack of abnormality at the neuromuscular junction (NMJ) of ErbB knockout animals (reviewed in Kummer et al. [2006]), the in vivo role of NRG/ErbB in synaptic transcription and the involvement of Cdk5 in neurotransmitter receptor transcription deserves further investigation. In addition to STAT3, Cdk5 may also affect gene transcription through the phosphorylation of another transcription factor MEF2. Phosphorylation of MEF2 by Cdk5 inhibits the transcriptional activity of MEF2 (reviewed in Cheung and Ip [2004]). Although modulation of MEF2 activity by Cdk5 has been associated with the regulation of neuronal death by Cdk5 and, recently, in the death of dopaminergic neuron in a model of Parkinson's disease (Smith et al., 2006), activity-dependent regulation of MEF2 activity also appears to affect the number of excitatory synapses (Flavell et al., 2006). This finding reveals an important role of MEF2 in the regulation of synapse remodeling, and it will be interesting to examine if MEF2 also takes part in the regulation of neurotransmitter receptor transcription at the synapse.

Regulation of Neurotransmitter Receptor Clustering

Efficient synaptic transmission relies on precise clustering of neurotransmitter receptors. The importance of Cdk5 in this process was recently demonstrated. PSD-95, the major scaffold protein in the postsynaptic densities (PSDs) of CNS synapses, was identified as a novel Cdk5 substrate. Cdk5-mediated phosphorylation of PSD-95 suppresses PSD-95 multimerization, thereby reducing PSD-95-dependent clustering of NMDA receptor subunit NR1 and voltage-gated K^+ channel Kv1.4. Indeed, $Cdk5^{-/-}$ cortical neurons exhibit marked enlargement of synaptic PSD-95 clusters, suggesting that Cdk5 is essential for clustering of PSD-95 in vivo (Morabito et al., 2004). The association of PSD-95 with a myriad of receptors and proteins at the PSD renders the regulation of PSD-95 multimerization by Cdk5 an important mechanism for affecting PSD composition. Further characterization of the downstream effects of PSD-95 phosphorylation may unravel more unanticipated involvements of Cdk5 in the modulation of PSD organization, as well as regulation of signaling cascades at the PSD.

Cdk5 also plays a potential role in AChR clustering and NMJ development. In vivo examination of the NMJ phenotype of Cdk5 knockout mice demonstrated that the bandwidth of AChR endplate is enlarged in $Cdk5^{-/-}$ diaphragm (Fu et al., 2005). Furthermore, AChR clusters are significantly larger in cultured myotubes lacking Cdk5 after agrin treatment, suggesting that Cdk5 may negatively regulate AChR cluster size (Fu et al., 2005; Lin et al., 2005). Additionally, Cdk5 was demonstrated to be required for ACh-induced dispersion of AChR clusters (Lin et al., 2005). ACh stimulation was observed to enhance Cdk5 activity in the myotubes, which in turn mediates the AChR cluster dispersing effect of ACh. These observations collectively reveal an unexpected role of Cdk5 in the regulation of AChR clustering at the NMJ (Figure 1).

Regulation of Dendritic Spine Remodeling

In addition to modulating the efficiency of synaptic transmission, regulation of dendritic spine morphology

constitutes another major mechanism by which synaptic plasticity is modulated. Because spine morphogenesis requires coordinated regulation of the cytoskeleton and adhesion protein, crucial modulators of actin dynamics such as Rho GTPases are indispensable in the regulation of spine morphology. Identification of the Rho GTPase Rac1 effector PAK1 as a substrate of Cdk5 (reviewed in Cheng and Ip [2003]) suggests that Cdk5 might regulate Rho GTPase activity. Recent identification of additional Rho GTPase regulatory factors as Cdk5 substrates lends further support to this hypothesis. GEFs (guanine nucleotide exchange factors) and GAPs (GTPase-activating protein) are regulatory factors exhibiting essential control on the duration of Rho GTPase activation. Although GEFs activate Rho GTPase by facilitating the exchange of GDP to GTP, GAPs facilitates inactivation of the enzyme by stimulating the GTP hydrolysis activity of Rho GTPase. Interestingly, the Rho GTPase Rac1 modulators GEF RasGRF2 and GAP α-chimaerin were both recently demonstrated as Cdk5 substrates (Kesavapany et al., 2004; Qi et al., 2004). Although phosphorylation of RasGRF2 by Cdk5 suppresses Rac activation (Kesavapany et al., 2004), Cdk5-mediated phosphorylation of α-chimaerin appears to have no effect on its Rac1-stimulating activity (Qi et al., 2004). Although the functional significance of α-chimaerin phosphorylation by Cdk5 remains to be determined, observations from these two studies suggest that Cdk5 may predominantly inhibit Rac1 activity through its phosphorylation of RasGRF2. It is also noteworthy that density of dendritic spines is enhanced in transgenic mice overexpressing p25, a truncated form of Cdk5 activator p35 predominating in pathological conditions (Fischer et al., 2005). Whether this is attributable to Cdk5-mediated regulation of Rho GTPase activity and whether Cdk5/p35 similarly exhibits stimulating effect on dendritic spines requires further characterization. Answers to these questions will be pivotal in delineating the precise involvement of Cdk5 in dendritic spine regulation.

Regulation of Neurotransmission

Through the modulation of DARPP-32 phosphorylation, Cdk5 has been established as an essential regulator of dopamine signaling. Phosphorylation of DARPP-32 at Thr34 by PKA is pivotal in the propagation of signaling downstream of dopamine D_1 receptor (D_1R) activation in the striatum. Phosphorylation of DARPP-32 at Thr75 by Cdk5, on the other hand, turns DARPP-32 into an inhibitor of PKA, thus dampening dopamine signaling (Bibb, 2003). Interestingly, recent advances in the field reveal that Cdk5 also affects dopamine signaling presynaptically. Tyrosine hydroxylase (TH), the rate-limiting enzyme in the synthesis of catecholamines including dopamine, was recently identified as a substrate of Cdk5 (Kansy et al., 2004; Moy and Tsai, 2004). Phosphorylation of TH by Cdk5 not only enhances total TH activity but also markedly elevates stability of the protein (Moy and Tsai, 2004). These observations implicate an important role of Cdk5 in modulating the production of dopamine. More importantly, inhibition of Cdk5 activity increases dopamine release in striatal slices (Chergui et al., 2004). The increased dopamine release results in elevated D_1R activation, and the downstream elevation of NMDA receptor activity. These observations collectively indicate that regulation of Cdk5 activity will likely have far-reaching consequences in dopamine signaling and the downstream interplay between dopamine and glutamate signaling in the striatum.

Cdk5 in Higher Cognitive Function and Neurodegenerative Diseases

An important development in the past few years is the increasing implication of Cdk5 involvement in a myriad of higher cognitive functions, neurodegenerative diseases, and drug-addiction-associated neuroadaptive changes. A number of studies have provided some much-needed insights on the in vivo role of Cdk5 in these complex functions.

Learning and Memory

Cdk5 was initially suggested to play a role in the regulation of synaptic plasticity through its phosphorylation of NMDA receptor subunit NR2A, where inhibition of Cdk5 activity suppresses NMDA-evoked currents and markedly attenuates LTP induction in CA1 hippocampal neurons. Furthermore, Cdk5 activity is enhanced during associative learning and fear conditioning (Fischer et al., 2003). Recent in vivo studies have provided further support for a pivotal role of Cdk5 in synaptic plasticity associated with learning and memory. For example, induction of LTD and spatial learning were both impaired in mice lacking p35 (Ohshima et al., 2005). In addition, the threshold for LTP induction was reduced in $p35^{-/-}$ mice (Wei et al., 2005). Furthermore, transient overexpression of p25 in transgenic mice enhances LTP and associative learning (Fischer et al., 2005). These observations collectively suggest that Cdk5 activity is crucial for synaptic plasticity, learning and memory in vivo.

Additional support for a role of Cdk5 in learning and memory came from the recently demonstrated importance of histone acetylation in memory and LTP formation. Structural remodeling of the chromatin, via acetylation and deacetylation of histones, has been associated with activation and silencing of gene expression, respectively. Two recent studies revealed that memory formation and LTP induction are accompanied by enhanced histone acetylation, with suppression of histone deacetylation markedly enhancing LTP induction and contextual fear conditioning in vivo (Alarcon et al., 2004; Levenson et al., 2004). Interestingly, mSds3, an essential component of the histone deacetylase1 (HDAC1) complex, was recently identified as a Cdk5 substrate. Cdk5-mediated phosphorylation of mSds3 results in diminished acetylation of histones, thus elevating mSds3-mediated transcriptional repression (Li et al., 2004). This suggests that Cdk5 may also affect memory formation and LTP induction through regulating histone deacetylation. Further investigation into this possibility may shed light on the mechanisms by which Cdk5 affects learning and memory.

Drug Addiction

Drug abuse is associated with modulation of dopamine signaling in the natural reward pathway. Interestingly, Cdk5 was recently demonstrated to take part in cocaine-induced changes in dopamine signaling. Chronic cocaine exposure leads to prolonged activation of PKA and accumulation of immediate early gene ΔFosB. This results in enhanced expression of Cdk5 and p35,

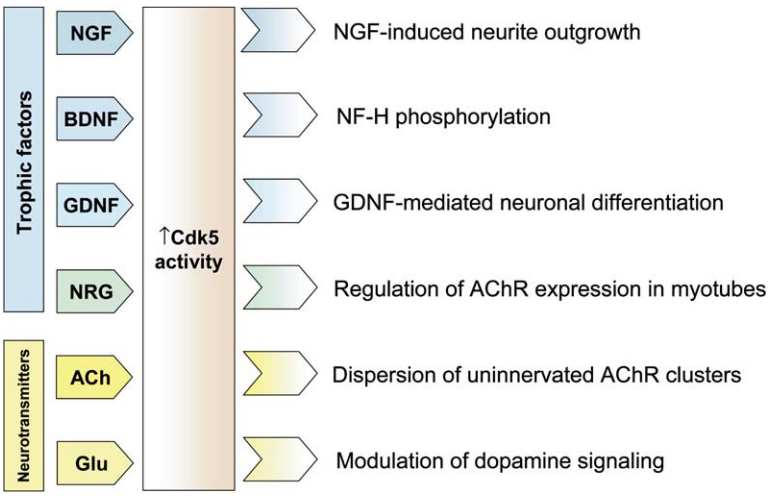

Figure 2. Signaling Pathways Implicated in the Regulation of Cdk5 Activity

Signaling pathways affected by Cdk5 in turn regulates Cdk5 activity. Trophic factors including NGF, BDNF, GDNF, and neuregulin (NRG) have all been observed to increase Cdk5 activity. In addition to trophic factors, neurotransmitters such as acetylcholine (ACh) and glutamate also enhance Cdk5 activity. The reported functional importance associated with the modulation of Cdk5 activity by the different factors is also indicated.

elevating Cdk5 activity. The augmented Cdk5 activity dampens the effect of chronic cocaine administration through inhibition of PKA activation (reviewed in Bibb [2003]). In transgenic mice overexpressing p35, elevation of Cdk5 activity attenuates cocaine-induced enhancement in Thr34 phosphorylated DARPP-32, downstream activation of Erk1/2, and the subsequent activation of transcription factor CREB (Takahashi et al., 2005). These observations underscore the in vivo functional significance of Cdk5 induction after chronic cocaine administration.

On the other hand, elevated Cdk5 activity also contributes to neuroadaptive changes such as regulation of dendritic spine morphology observed during chronic cocaine administration (Bibb, 2003; Norrholm et al., 2003). A recent study revealed that histone acetylation serves as an essential mechanism by which chronic cocaine exposure results in neuroadaptive changes (Kumar et al., 2005). Chronic cocaine stimulation leads to histone acetylation of certain gene promoters including that of Cdk5, thereby enhancing gene transcription. Findings from this study not only verify that Cdk5 is induced by chronic cocaine exposure via ΔFosB in vivo but also reveal that cocaine-induced transcriptional and behavioral changes both required histone acetylation (Kumar et al., 2005). Further delineation on the precise role of Cdk5 activity in chronic cocaine-induced neuroadaptive changes is clearly needed. Moreover, whether Cdk5-mediated regulation of HDAC complex also contributes to cocaine-induced modification of histones awaits further investigation.

Alzheimer's Disease

Cdk5 has long been implicated in the pathophysiology of Alzheimer's Disease (AD). Deregulation of Cdk5 activity and calpain-mediated cleavage of p35 into p25 has been observed in AD brains (reviewed in Cruz and Tsai [2004]). Indeed, it was recently demonstrated that prolonged induction of p25 expression results in impaired spatial learning, accompanied by brain atrophy and hippocampal neuronal loss (Fischer et al., 2005), thus consolidating the potential involvement of Cdk5/p25 in the pathophysiology of AD. Nonetheless, although most AD studies have focused on neuronal loss being the major cause of dementia, increasing studies suggest that synapse loss prior to neurodegeneration may provide a better correlation with function loss in AD patients. A recent study revealed that synaptic loss might in part be accounted for by Aβ-induced reduction of NMDA receptor (Snyder et al., 2005) and surface AMPA receptor (Roselli et al., 2005). It therefore appears that Aβ may directly affect synaptic transmission through modulation of glutamatergic synapse composition. Remarkably, reduction of surface AMPA receptor is dependent on calcium influx through the NMDA receptor and Cdk5-mediated degradation of PSD-95 (Roselli et al., 2005). The precise involvement of glutamate signaling and Cdk5 signaling in synaptic functions associated with AD will undoubtedly remain an important area of research.

Future Perspectives

In this communication, we have reviewed the latest progress on the role of Cdk5 as a key regulator of synaptic transmission and synaptic plasticity. Progress from the past 2 years have not only consolidated the importance of Cdk5 in the regulation of synaptic transmission through the identification of novel substrates but have also provided in vivo evidence for an important role of Cdk5 in the regulation of learning, memory formation, and drug addiction. These recent advancements in the field have highlighted several emerging themes in Cdk5 research deserving our continued effort and attention.

First of all, elucidation of the biological functions of Cdk5 has relied almost exclusively on the identification of its substrates. Although this approach has undoubtedly led to many interesting and important revelations on the functional role of Cdk5, our knowledge on the biological actions of Cdk5 in vivo are lagging behind. Future studies directed to elucidating the in vivo actions of Cdk5 will immensely expand our understanding on the biological functions of Cdk5. For example, recent studies with transgenic animals have associated Cdk5 with an increasing number of higher brain functions and neurodegenerative disease such as drug addiction, spatial learning, memory formation, and Alzheimer's disease. In addition, the exhibition of aberrant excitatory feedback circuit and spontaneous seizure in $p35^{-/-}$ mice (Patel et al., 2004) reveals that Cdk5 may also contribute to seizure activity. Continued efforts in elucidating the importance of Cdk5 in these complex functions, and delineation of the mechanisms implicated, will be

pivotal in providing us with a more complete picture of Cdk5 action in higher brain functions in vivo.

Cdk5 is potentially involved in several neurological and psychiatric disorders. Implication of Cdk5 in neuronal death associated with Alzheimer's and Parkinson's disease reveals Cdk5 as a key player in the pathophysiology of these neurodegenerative diseases. With the increasing implication of synaptic dysfunction in the progress of these neurological disorders, whether Cdk5 affects neurotransmission prior to neuronal death deserves further elucidation. Moreover, aberrant synaptic transmission is also associated with the psychological disorder schizophrenia. Abnormalities in dopamine, glutamate, acetylcholine, and GABAergic neurotransmission have all been demonstrated in schizophrenia patients. Given the regulatory role of Cdk5 in dopamine and ErbB signaling, it would be of interest to examine if Cdk5 also modulates the onset and progression of schizophrenia. The increasing implication of Cdk5 in a myriad of neurological and psychiatric disorders, and the observed regulation of dopamine release by Cdk5, for example, may render Cdk5 a potential target for therapeutic treatment for neurodegenerative diseases such as Parkinson's disease. Further investigation on the involvement of Cdk5 in these disorders will not only enhance our understanding of this multifaceted kinase but may also provide novel insights into the treatment of these disorders.

Finally, although a majority of the studies have focused on the downstream functions of Cdk5, how Cdk5 activity is regulated is not well understood. Although several studies have identified pathways that affect Cdk5 activity (Figure 2), the mechanisms implicated require further exploration. Interestingly, a number of trophic factors including nerve-growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell-line-derived neurotrophic factor (GDNF), and NRG have all been observed to increase Cdk5 activity (Cheng and Ip, 2003; Dhavan and Tsai, 2001; Ledda et al., 2002). In addition, recent studies revealed that Cdk5 activity is also enhanced by neurotransmitters such as ACh and glutamate (Bibb, 2003; Lin et al., 2005; Wei et al., 2005). Because receptor tyrosine kinases (RTKs) serve as cognate receptors for a number of trophic factors and have also been observed to modulate synaptic transmission, elucidating the interplay between RTKs and Cdk5 may shed light on the mechanisms by which these pathways result in the regulation of Cdk5 activity. Regardless, given the increasing implication of Cdk5 as a key regulator of synaptic functions, our understanding on the biological roles of Cdk5 at synapse will clearly be far from complete without further characterization of the pathways involved in the regulation of Cdk5 activity. More importantly, with the recent association of Cdk5 with a number of neurodegenerative diseases, this information will be invaluable in the development of therapeutic treatment for these neurodegenerative diseases.

Selected Reading

Alarcon, J.M., Malleret, G., Touzani, K., Vronskaya, S., Ishii, S., Kandel, E.R., and Barco, A. (2004). Neuron *42*, 947–959.

Bibb, J.A. (2003). Neurosignals *12*, 191–199.

Cheng, K., and Ip, N.Y. (2003). Neurosignals *12*, 180–190.

Chergui, K., Svenningsson, P., and Greengard, P. (2004). Proc. Natl. Acad. Sci. USA *101*, 2191–2196.

Cheung, Z.H., and Ip, N.Y. (2004). Neurosci. Lett. *361*, 47–51.

Cruz, J.C., and Tsai, L.H. (2004). Trends Mol. Med. *10*, 452–458.

Dhavan, R., and Tsai, L.H. (2001). Nat. Rev. Mol. Cell Biol. *2*, 749–759.

Fischer, A., Sananbenesi, F., Spiess, J., and Radulovic, J. (2003). Neurosignals *12*, 200–208.

Fischer, A., Sananbenesi, F., Pang, P.T., Lu, B., and Tsai, L.H. (2005). Neuron *48*, 825–838.

Flavell, S.W., Cowan, C.W., Kim, T.K., Greer, P.L., Lin, Y., Paradis, S., Griffith, E.C., Hu, L.S., Chen, C., and Greenberg, M.E. (2006). Science *311*, 1008–1012.

Fu, A.K., Fu, W.Y., Cheung, J., Tsim, K.W., Ip, F.C., Wang, J.H., and Ip, N.Y. (2001). Nat. Neurosci. *4*, 374–381.

Fu, A.K., Fu, W.Y., Ng, A.K., Chien, W.W., Ng, Y.P., Wang, J.H., and Ip, N.Y. (2004). Proc. Natl. Acad. Sci. USA *101*, 6728–6733.

Fu, A.K., Ip, F.C., Fu, W.Y., Cheung, J., Wang, J.H., Yung, W.H., and Ip, N.Y. (2005). Proc. Natl. Acad. Sci. USA *102*, 15224–15229.

Kansy, J.W., Daubner, S.C., Nishi, A., Sotogaku, N., Lloyd, M.D., Nguyen, C., Lu, L., Haycock, J.W., Hope, B.T., Fitzpatrick, P.F., and Bibb, J.A. (2004). J. Neurochem. *91*, 374–384.

Kesavapany, S., Amin, N., Zheng, Y.L., Nijhara, R., Jaffe, H., Sihag, R., Gutkind, J.S., Takahashi, S., Kulkarni, A., Grant, P., and Pant, H.C. (2004). J. Neurosci. *24*, 4421–4431.

Kumar, A., Choi, K.H., Renthal, W., Tsankova, N.M., Theobald, D.E., Truong, H.T., Russo, S.J., Laplant, Q., Sasaki, T.S., Whistler, K.N., et al. (2005). Neuron *48*, 303–314.

Kummer, T.T., Misgeld, T., and Sanes, J.R. (2006). Curr. Opin. Neurobiol. *16*, 74–82.

Ledda, F., Paratcha, G., and Ibanez, C.F. (2002). Neuron *36*, 387–401.

Lee, S.Y., Wenk, M.R., Kim, Y., Nairn, A.C., and De Camilli, P. (2004). Proc. Natl. Acad. Sci. USA *101*, 546–551.

Lee, S.Y., Voronov, S., Letinic, K., Nairn, A.C., Di Paolo, G., and De Camilli, P. (2005). J. Cell Biol. *168*, 789–799.

Levenson, J.M., O'Riordan, K.J., Brown, K.D., Trinh, M.A., Molfese, D.L., and Sweatt, J.D. (2004). J. Biol. Chem. *279*, 40545–40559.

Li, Z., David, G., Hung, K.W., DePinho, R.A., Fu, A.K., and Ip, N.Y. (2004). J. Biol. Chem. *279*, 54438–54444.

Lin, W., Dominguez, B., Yang, J., Aryal, P., Brandon, E.P., Gage, F.H., and Lee, K.F. (2005). Neuron *46*, 569–579.

Liu, Y., Cheng, K., Gong, K., Fu, A.K., and Ip, N.Y. (2006). J. Biol. Chem., in press. Published online February 6, 2006. 10.1074/jbc.M513496200.

Morabito, M.A., Sheng, M., and Tsai, L.H. (2004). J. Neurosci. *24*, 865–876.

Morgan, J.R., Di Paolo, G., Werner, H., Shchedrina, V.A., Pypaert, M., Pieribone, V.A., and De Camilli, P. (2004). J. Cell Biol. *167*, 43–50.

Moy, L.Y., and Tsai, L.H. (2004). J. Biol. Chem. *279*, 54487–54493.

Norrholm, S.D., Bibb, J.A., Nestler, E.J., Ouimet, C.C., Taylor, J.R., and Greengard, P. (2003). Neuroscience *116*, 19–22.

Ohshima, T., Ogura, H., Tomizawa, K., Hayashi, K., Suzuki, H., Saito, T., Kamei, H., Nishi, A., Bibb, J.A., Hisanaga, S., et al. (2005). J. Neurochem. *94*, 917–925.

Patel, L.S., Wenzel, H.J., and Schwartzkroin, P.A. (2004). J. Neurosci. *24*, 9005–9014.

Qi, R.Z., Ching, Y.P., Kung, H.F., and Wang, J.H. (2004). FEBS Lett. *561*, 177–180.

Roselli, F., Tirard, M., Lu, J., Hutzler, P., Lamberti, P., Livrea, P., Morabito, M., and Almeida, O.F. (2005). J. Neurosci. *25*, 11061–11070.

Smith, P.D., Mount, M.P., Shree, R., Callaghan, S., Slack, R.S., Anisman, H., Vincent, I., Wang, X., Mao, Z., and Park, D.S. (2006). J. Neurosci. *26*, 440–447.

Snyder, E.M., Nong, Y., Almeida, C.G., Paul, S., Moran, T., Choi, E.Y., Nairn, A.C., Salter, M.W., Lombroso, P.J., Gouras, G.K., and Greengard, P. (2005). Nat. Neurosci. *8*, 1051–1058.

Takahashi, S., Ohshima, T., Cho, A., Sreenath, T., Iadarola, M.J., Pant, H.C., Kim, Y., Nairn, A.C., Brady, R.O., Greengard, P., and Kulkarni, A.B. (2005). Proc. Natl. Acad. Sci. USA *102*, 1737–1742.

Tan, T.C., Valova, V.A., Malladi, C.S., Graham, M.E., Berven, L.A., Jupp, O.J., Hansra, G., McClure, S.J., Sarcevic, B., Boadle, R.A., et al. (2003). Nat. Cell Biol. *5*, 701–710.

Tomizawa, K., Sunada, S., Lu, Y.F., Oda, Y., Kinuta, M., Ohshima, T., Saito, T., Wei, F.Y., Matsushita, M., Li, S.T., et al. (2003). J. Cell Biol. *163*, 813–824.

Wei, F.Y., Tomizawa, K., Ohshima, T., Asada, A., Saito, T., Nguyen, C., Bibb, J.A., Ishiguro, K., Kulkarni, A.B., Pant, H.C., et al. (2005). J. Neurochem. *93*, 502–512.

Xie, F., Raetzman, L.T., and Siegel, R.E. (2004). J. Neurochem. *90*, 1521–1529.