IJMPR 2023, 7(6), 04-11

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article

SJIF Impact Factor: 5.273

AN OVERVIEW OF CYCLIN-DEPENDENT KINASE 5: A NOVEL PHARMACOLOGICAL TARGET FOR NEURODEGENERATIVE DISEASES

Fasna V*, Bijesh vatakkeel[1], R. Raji[2] and Adhya Das[3]

[1]Assistant Professor, Department of Pharmacology, College of Pharmaceutical Sciences, Govt. Medical College, Kannur, Pariyaram, 670503.

[2,3]IV[th] Semester M. Pharm Student, Department of Pharmacology, College of Pharmaceutical Sciences, Govt. Medical College, Kannur, Pariyaram, 670503.

Received on: 30/03/2023

Revised on: 20/04/2023

Accepted on: 10/05/2023

***Corresponding Author**

Fasna V.

IV[th] Semester M. Pharm Student, College of Pharmaceutical Sciences, Govt. Medical College, Kannur, Pariyaram, 670503.

ABSTRACT

Cyclin-dependent kinase 5 (Cdk5) is a member of a family of proline-directed serine/threonine kinase. Cdk5 plays a critical role in the development of the nervous system, including neuronal migration and differentiation. Unlike the other Cdk family members, Cdk5 is neither directly engaged in cell cycle regulation nor is it controlled by cyclins. Dopaminergic signalling, release of neurotransmitters, membrane cycling and other synaptic functions are all impacted by Cdk5. The two Cdk5 activators are p35 and p39, which control the spatial and temporal expression of active Cdk5 in order to limit its activity largely to post-mitotic neurons. Despite playing a crucial part in central nervous system development, dysregulation of Cdk5 has been linked to a number of diseases including Alzheimer's disease, Amyotrophic lateral sclerosis, Parkinson's disease etc. When Cdk5 is associated with p25, a shortened version of the typical activator p35, it becomes overactivated and relocalizes in these neurodegenerative diseases, ultimately resulting in neuronal death. It is important to note that Cdk5 inhibitors have been demonstrated to have neuroprotective benefits by preventing associated degenerative processes. With a focus on current developments in Cdk5 in neurological illnesses and the possibility of targeting Cdk5 for the treatment of neurological disorders, this review will briefly describe the physiological and pathological mechanisms of Cdk5 in the nervous system.

KEYWORDS: Cdk5, p35, p25, Cyclins, Neurological disorders, CDK5 inhibitors.

INTRODUCTION

Neurodegenerative disease is a heterogeneous group of disorders that are caused by the degradation and subsequent loss of neurons. These changes in the human brain can lead to cognitive or functional decline of the patient over time. While some neurodegenerative diseases can be due to genetic mutations, some are also associated with hazardous living environments. However, some of the causes are still unknown. Different types of neurodegenerative disorders are Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD), and amyotrophic lateral sclerosis (ALS). Since many neurological disorders are late-onset diseases, their occurrence will rise in very large numbers over the next century. These diseases presents a major health and financial burden to every health service organization in the world.[1]

In neurons, a number of cellular functions are controlled by the proline-directed serine/threonine protein kinase known as cyclin-dependent kinase 5 (CDK5). Cdk5 was first identified two decades ago based on its high sequence homology to a key regulator of cell cycle progression, cell division cycle protein 2 (Cdc2, also known as Cdk1). Despite having a 60% sequence identity with Cdc2 and retaining the primary structural features of Cdks, Cdk5 is distinct from the other members of the Cdk family since it is neither significantly involved in cell cycle regulation nor is it activated by cyclins. Cdk5 preferentially phosphorylates substrates at the S/T sites within a consensus motif (S/T) PX(K/H/R), where S/T represents the phosphorylatable serine/threonine residue, P is the required proline residue, X stands for any amino acid, and K/H/R represents a basic residue. Similar to other Cdks, monomeric Cdk5 requires connection with either p35 or p39, two proteins that function as its regulatory subunits, in order to be activated. Although Cdk5 is ubiquitously expressed in all tissues, its activity is mostly restricted to the nervous system where p35 and p39 are predominately expressed, in agreement with the critical roles of p35 or p39 in activating Cdk5.[2]

Cdk: Structure and Activity

CDKs are serine/threonine protein kinases that phosphorylate serine or threonine residues followed by proline ([S/T]P motif). Target protein serine or threonine

residues have side-chain hydroxyl groups, and CDK molecules catalyse the transfer of ATP's -phosphate onto those groups. The "catalytic core" of protein kinases, which makes up the majority of CDKs, is about 300 amino acids long and is not extended by N- or C-terminal extensions (Figure 1). They exhibit the same fold as the large family of serine/threonine protein kinases, tyrosine protein kinases, and certain phospholipid kinases, including phosphatidylinositol 3 (PI3) kinase. This fold is formed from an N-terminal domain of approximately 85 amino acids composed largely of β-sheet, and a C-terminal domain (CTD) of approximately 215 amino acids composed primarily of α-helix. Peptide substrates bind mostly with the CTD while ATP is bound between these two domains. A sequence of amino acids known as the activation segment or T-loop, which is found in human CDK2 residues 145–172, is necessary for the binding of both nucleotide and peptide substrates. Sequence similarity and cyclin binding's necessity for complete activity are the characteristics that distinguish CDKs.[3]

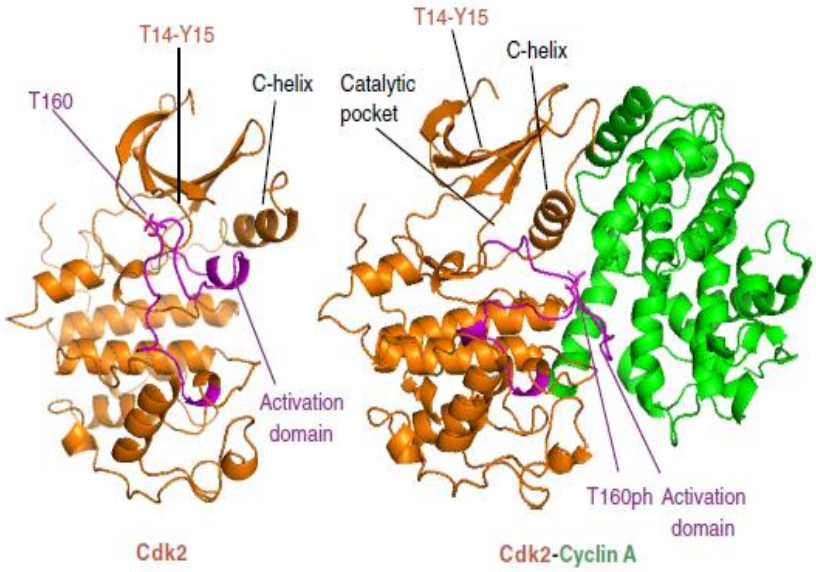

Figure 1: A three-dimensional view of CDK structure and activation.

Regulation of Cdk5: regulatory subunit

There are 21 members of the Cdk family, and the majority of them need to associate with particular cyclin partners in order to become constitutively active protein kinases. Surprisingly, p35, a protein that is not a cyclin, is the subunit necessary for Cdk5 action. The Cdk5 regulatory component p35 was discovered to be absent from the conserved amino acid sequences commonly present in cyclins. In brain lysates, p35 physically binds with Cdk5 and, upon direct binding, can activate Cdk5.[4]

Its high degree of sequence identity to p35 led to the later discovery of p39, another Cdk5 regulatory component. While p35 and p39 have many similarities, such as high levels of expression in the brain, direct binding to Cdk5, and the capacity to activate Cdk5, they also differ in certain ways. When it comes to brain development, p35 expression is high from the embryonic stage through the postnatal stage, but p39 expression only begins to rise postnatally. Regional distribution patterns for p35 and p39 differ; p35 is expressed most strongly in the cerebral cortex and cerebellum, whereas p39 is strongly expressed in the cerebellum, spinal cord and brain stem. Furthermore, compared to p35, the p39 protein exhibits increased protein stability and reduced Cdk5 binding affinity. Despite their redundant functions in the nervous system, studies have found that Cdk5/p39 preferentially regulates some functions while Cdk5/p35 does not. While no abnormalities was seen in cultured neurons missing p35 expression, deletion of p39 or Cdk5 results in impaired dendritic formation.[5]

Roles of Cdk5 in the nervous system

***Neuronal migration**

Gene-targeting experiments show that Cdk5 is involved in the development of the brain, notably in neuronal migration. Multiple mechanisms are used by Cdk5 to control neuronal migration. N-cadherin adhesion complex interacts with Cdk5/p35. Neuronal migration is hampered by increased N-cadherin-mediated cell adhesion, which is enhanced by pharmacological suppression of Cdk5.[6]

***Neurite outgrowth**

To develop neurites and generate axons, Cdk5 is necessary. When Cdk5 is inactivated in cultured neurons, neurite outgrowth is inhibited and Cdk5 and p35 colocalize with actin filaments in axonal growth cones. The length of the neurites in cultured neurons, however, increases when Cdk5 and p35 are co-expressed.[7]

***Synaptic plasticity**

The development of memories depends on synaptic plasticity, which is the alteration of the efficacy or

intensity of synaptic transmission in response to neuronal activity. Numerous processes operate at pre- and post-synaptic levels to control synaptic plasticity. Cdk5 modulates Ca2+ influx, endocytosis, and exocytosis presynaptically.[8]

***Synaptic homeostasis**

A compensating mechanism, synaptic homeostasis enables neurons to adjust to changed levels of network activity. When inputs are muted, neurons potentiate synaptic effectiveness, and when inputs are amplified, neurons down regulate their activity. Thus, despite frequent changes in input activity, homeostatic processes keep neuron's firing rates within a desirable range and defend network stability.[9]

Cdk5 IN NEURODEGENERATIVE DISEASES

Although Cdk5 activity is essential for proper CNS development and a number of other crucial physiological nervous system activities, it has been demonstrated that dysregulation of this kinase plays a role in the neurodegenerative processes of a number of illnesses.[10]

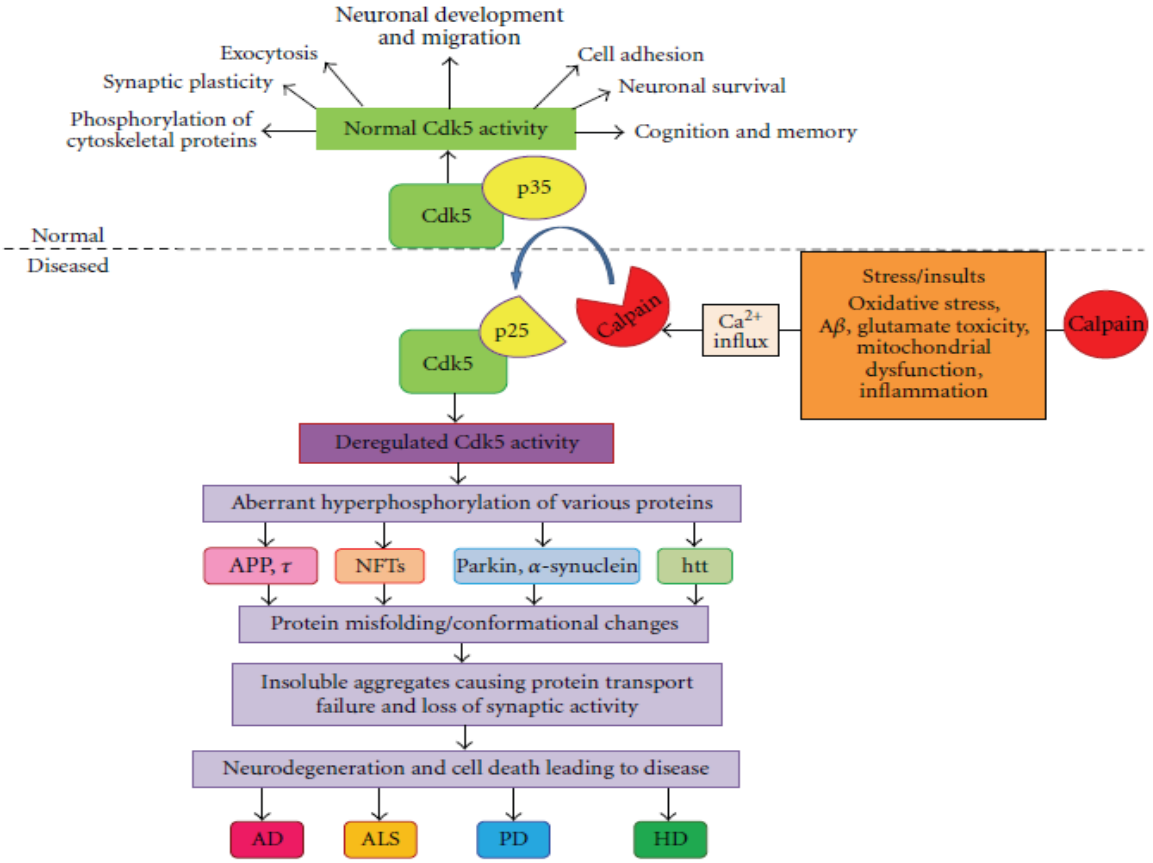

Figure 3: Role of Cdk5 in physiology and pathology of various neurodegenerative Diseases.

Alzheimer's Disease (AD)

The most prevalent form of dementia, Alzheimer's disease (AD), is identified by three key symptoms: the buildup of amyloid plaques, the development of neurofibrillary tangles, and severe selective neuronal loss.[11] The understanding of Cdk5's role in the pathophysiology of Alzheimer's disease has advanced significantly. Cdk5 activation is harmful to cultured neurons and may be the cause of disease-related neurodegeneration. The calcium-activated protease calpain can catalytically cleave the unstable isoform p35 to produce the hyperactive isoform p25.[12] According to this result, AD brains had higher amounts of p25 and activated calpain. Direct Cdk5 inhibition was demonstrated to reduce Aβ neurotoxicity [13] or by interfering with the production of p25 via upstream action on calpain activation.[14]

The oligomeric form of Aβ has been proposed as the primary mediator of its toxicity. Aβ is produced through the successive amyloidogenic cleavage of the precursor protein APP by the β-secretases BACE1 and $_{\gamma}$-secretase.[15] The APP gene or the genes encoding presenilins 1 (PS1) and 2 (PS2), two proteins that are a component of the β-secretase complex, are the sites of all mutations that are currently known to cause AD.[16] Dysregulated Cdk5 regulates the processing of APP and boosts the synthesis of Aβ by phosphorylating it at Thr668. [17] In fact, a recent study found that specific inhibition of Cdk5-p25 inhibits the loss of cortical neurons caused by Aβ. According to studies, Cdk5/p25 increases Aβ synthesis by STAT3-mediated transcriptional control of BACE1. Cdk5/p25 phosphorylates STAT3 at the S727 residue, activating BACE1 transcription in the process. The Cdk-p25 mouse

brain exhibits a substantial increase in BACE1 immunoreactivity and APP β-secretase processing.[18] Additionally, Cdk5 phosphorylates APP at T668, which makes it easier for BACE1 to cleave APP and enhance the production of Aβ.[19]

Tau is a microtubule-associated protein that stabilises neuronal microtubules and controls microtubule dynamics involved in axonal outgrowth and transport.[20] Tau protein kinase Cdk5 phosphorylates tau in vitro. Compared to overexpression of the Cdk5/p35 complex, overexpression of Cdk5/p25 causes an increase in tau phosphorylation in cultured neurons. Hyper phosphorylation, on the other hand, causes tau to lose its association with microtubules and to accumulate into filaments and tangles, which ultimately results in synapse loss and neuronal death.[21] In mice models of P301L and P301S tauopathy, increased calpain activity, p25 protein buildup, and Cdk5 hyperactivity have been noted.[22] In mice expressing tau P301L, pharmacological suppression of calpain by calpastatin lowers tau phosphorylation/aggregation and slows the course of illness.[23]

Parkinson's' disease (PD)

Parkinson's disease (PD), a long-term movement illness, is characterised by the development of Lewy bodies, mitochondrial dysfunction, and dopaminergic neuron loss in the substantia nigra.[24] Recent investigations have shown that Cdk5 is involved in the process even though the precise mechanism of dopaminergic neuronal death is still unknown.[25]

The loss of dopaminergic neurons and the development of PD are thought to be connected by a dysregulation of Cdk5. In early-stage PD, abnormal p25/Cdk5 signalling was discovered. Previous research shown that Cdk5 might increase oxidative stress, which then causes mitochondrial malfunction and autophagy dysfunction in people with Parkinson's disease (PD).[26] The MPTP mouse model has revealed enhanced p25 production and upregulated Cdk5 expression/activity.[27] In pharmacological animal models of the disease, particularly those corresponding to the administration of MPTP, as well as in the brains of PD patients, it was discovered that the activity and levels of this kinase were altered.[28] Given that MPTP treatment significantly raises glutamate levels, an imbalance in calcium and subsequent calpain activation result from the imbalance, this process most likely involves glutamate excitotoxicity.[29]

Numerous studies connect PD's oxidative stress and Cdk5 hyperactivity. Reactive oxygen species (ROS), which are byproducts of typical mitochondrial metabolism, can harm lipids, proteins, and DNA and obstruct a variety of cellular functions.[30] Studies continue to show that Cdk5 may affect cellular defences against oxidative stress, which may contribute to the pathophysiology of Parkinson's disease. In reaction to MPTP or MPP+ treatment, Cdk5 phosphorylates the antioxidant peroxidase peroxiredoxin 2 (Prx2) to decrease its activity. More significantly, the protective effect of Prx2 against MPP+-induced cell death is drastically diminished when a phosphomimetic mutant of Prx2 is overexpressed.[31] By impeding DNA damage repair, which is frequently prompted by oxidative stress and can result in cell death, Cdk5 also worsens oxidative stress in MPTP or MPP+ treated cells. The DNA repair enzyme a purinic/a pyrimidinic endonuclease 1 (Ape1) is phosphorylated by Cdk5 and loses some of its activity as well as its ability to protect neurons against MPTP toxicity. Collectively, our results indicate that, in models of Parkinson's disease, unregulated Cdk5 impairs cellular antioxidative defence, which leads to neuronal death.[32]

Parkin dysfunction and mitochondrial abnormalities are two additional routes for Cdk5 hyperactivity in PD development that have been proposed. Parkin and α-synuclein have both been linked to phosphorylation by Cdk5.[33] Parkin functions as an E3 ubiquitin ligase, a component of the ubiquitin-proteasome system, whereas α-synuclein is the main component of Lewy bodies and is typically found in neural tissue where it is known to play a role in neurotransmission.[34] The phosphorylation of Drp1 by aberrant Cdk5 in a non-human primate model of Parkinson's disease is thought to speed up neurotoxicity and mitochondrial dysfunction.[35] Parkin malfunction is hypothesised to control the progression of Parkinson's disease (PD), as Parkin mutations have been found in people with the autosomal recessive type of the disease. In the brains of people with Parkinson's disease, there is decreased Parkin activity and evidence of Parkin aggregates in the Lewy body. Numerous studies demonstrate that Parkin's ubiquitin ligase activity is noticeably decreased and Parkin aggregation is increased when Cdk5 phosphorylates it at S131, which results in neurotoxicity.[36] Together, our results highlight the roles played by oxidative stress, mitochondrial abnormalities, and Parkin dysfunction in the aetiology of Parkinson's disease (PD).

Amyotrophic lateral sclerosis (ALS)

A neurodegenerative condition called amyotrophic lateral sclerosis (ALS) causes the selective death of motor neurons in the cerebral cortex, brainstem, and spinal cord. Large-caliber axons, a property that depends on neurofilaments, are a distinctive feature of motor neurons.[37] In individuals with sporadic ALS and in an instance of familial ALS with a defective superoxide dismutase type 1 (SOD1) gene, degenerating neurons in the spinal cord showed high Cdk5 positivity.[38] Furthermore, it has been demonstrated that the SOD1G93A mouse model of ALS exhibits hyperphosphorylation of tau and neurofilament(NF) as well as p25 accumulation and Cdk5 hyperactivity in its spinal cord. Cdk5 activity interestingly corresponds with lethality in the two lines of SOD1G37R mice with varied disease severity. In contrast, reducing Cdk5 hyperactivity

helps SOD1G93A animals with motor impairments, delays pathology, and lengthens survival.[39]

Huntington's disease (HD)

Huntington's disease (HD) is an autosomal dominant illness with a mix of motor, cognitive, and behavioural traits. HD is brought on by polyglutamine (polyQ)-encoding extended CAG trinucleotide repeats in the huntingtin gene (HTT).[40] It has been demonstrated that Cdk5 is involved in the pathogenic process. It was hypothesised that Cdk5, in contrast to AD and PD, had neuroprotective effects in HD. Other research, however, have shown outcomes that differ.[41] In Huntington's disease, excessive cleavage of mutant antiapoptotic huntingtin protein (mHTT) by caspases, calpains, and aspartic proteases results in the buildup of toxic fragments that eventually destroy motor cortex neurons and cause degeneration in striatal neurons.[42] According to recent research, Huntington's disease Cdk5p35 activation protects neurons. It has been demonstrated that Cdk5p35 inhibits mHTT aggregation by phosphorylating mHTT, greatly lowering polyQ cleavage, accumulation, and ensuing toxicity.[43] Additionally, it has been demonstrated that in response to DNA damage, both in vivo and in vitro, Cdk5 phosphorylates mHTT at Ser1181 and Ser1201, reducing polyQ-induced p53-mediated toxicity and cell death in striatal neurons.[44] In addition, mHTT aggregation requires the presence of intact microtubule cytoskeletons. As was noted earlier, MAPs are phosphorylated by Cdk5 to control the stability of the microtubule network.

In line with the disruption of the microtubule network, it has been demonstrated that Cdk5p35 inhibits mHTT inclusion in primary neurons.[45] Low Cdk5 and p35 levels have been seen in the striatum of mutant mice and post-mortem HD patients. Increased mHTT levels are associated with decreased Cdk5 expression, decreased Cdk5 activity, and increased p35 to p25 conversion, suggesting that mHTT may be a potential Cdk5 pathway modulator. HD pathophysiology may be influenced by both decreased Cdk5p35 activity and increased Cdk5p25 activity. Treatments for the condition that mimic, promote, or block Cdk5p35 activity or inhibit Cdk5p25 activity may be helpful.[46]

Multiple sclerosis (MS)

The transformation of adult oligodendrocyte precursor cells into mature oligodendrocytes is controlled by Cdk5, which is crucial. Cdk5 is crucial for the oligodendrocytes' development of the myelin sheath. Diseases associated with demyelination, such as multiple sclerosis, can be brought on by abnormal Cdk5 activity.[47] In a multiple sclerosis mouse model, oligodendrocyte Cdk5 activation induces demyelination and impairs cognition. It is yet unknown what exactly causes Cdk5 to function in multiple sclerosis. The regulation of lymphocyte activation by Cdk5 has been demonstrated to contribute to the pathological development of multiple sclerosis.[48]

CDK5 AS A TARGET FOR DISEASE TREATMENT

Cdk5 is a desirable therapeutic target for these indications because of its capacity to direct the pathogenic processes that result in the development of neurodegenerative disease. However, because to the complicated physiological role that Cdk5-p35 plays in the adult brain, it is essential to specifically inhibit the Cdk5-p25 complex in order to eliminate Cdk5's pathogenic characteristics while maintaining its normal function. Although the literature has identified the following three kinds of Cdk5 inhibitors as inhibiting Cdk5p25 activity, to our knowledge, no specific Cdk5 inhibitor has ever entered clinical trials.

- Targeting ATP Binding and Non ATP Binding Regions on Cdk5- The ATP-binding areas of the kinases are the target of current methods for producing kinase activity inhibitors. Due to similarities in amino acid sequences in the ATP binding region, it is difficult to achieve good selectivity for Cdk5 over other Cdks using this method. Due to off-target toxic effects and significant side effect profiles, non-selective Cdk inhibitors are typically undesirable and ineffective and prevent dose escalation.[49]
- Peptides inhibitors- The 125 amino acid peptide known as Cdk5 inhibitory peptide (CIP), which is generated from p35, has a higher affinity for Cdk5 than p25 or p35 but is unable to activate Cdk5 in vitro, leading to competitive inhibition of Cdk5. The activity of Cdk5p25 in cortical neurons was found to be exclusively and effectively inhibited by CIP, with no impact on Cdk5p35 or other Cdk activities, or endogenous Cdk5p25 activity.[50] Overexpressing CIP in the p25 transgenic mouse model inhibits Cdk5 hyperactivation and decreases the buildup of A and phosphorylated tau levels. In p25 transgenic mice, CIP overexpression also prevents neuronal loss and enhances memory performance.[51]
- Small Molecules inhibitors- In order to stop the interactions between Cdk5 and p25, small molecule protein–protein interaction (PPI) inhibitors have recently been researched. Assays based on protein–protein interactions offer a viable method for finding new PPI inhibitors of the Cdk5–p25 interaction.[52]

CONCLUSION

Neurological disorders are a group of disorders with sensory, motor or cognitive damage, caused by dysfunction of the central or peripheral nervous system. Normal brain function is compromised by the dysregulation of Cdk5, a proline-directed serine/threonine protein kinase that controls a number of cellular processes in neurons. In general, recent years have seen significant advancements in our knowledge of Cdk5's role in neurological illnesses. Numerous investigations have supported both its crucial physiological role and, after being overactivated, its harmful effects.

The normal growth of the mammalian central nervous system depends on the activity of cyclin-dependent kinase 5 (Cdk5) and its regulatory component p35. p35 is converted to p25 through proteolytic cleavage, which causes abnormal Cdk5 activation. p25 buildup has been linked to a number of neurodegenerative conditions, including AD and PD. The p25/Cdk5 complex causes neurodegeneration through a number of distinct pathways when Cdk5 activity is dysregulated in pathological or disease-related circumstances. Excessive Cdk5 activity has been linked to neuronal loss brought on by excitotoxicity, ischemia, and oxidative stress, as well as in animal models of neurodegenerative disorders including Alzheimer's and Parkinson's. The brains of people with Alzheimer's disease (AD) have been found to have higher quantities of the protein p25, which when overexpressed leads to the pathological hallmarks of AD—phosphorylated tau, neurofibrillary tangles, and cognitive impairments. Additionally, p25/Cdk5 hyperphosphorylates neurofilament proteins, which are pathogenic indicators of amyotrophic lateral sclerosis and Parkinson's disease. The discovery of successful therapeutic approaches resulting from the dysregulation of Cdk5 in disorders including AD, HD, PD, and amyotrophic lateral sclerosis may benefit from targeting these regulators as a different approach.

These broad-spectrum Cdk5 inhibitors are not without drawbacks in an in vivo setting. Therapeutic benefit would result from blocking aberrantly active Cdk5/p25 without affecting Cdk5/p35. Unless strategies are developed to ensure focused, efficient distribution to the brain, peptides are unlikely to be successful in vivo. Moving forward, a possible approach to meet the criteria for a successful Cdk5 inhibitor is to develop small molecule PPI inhibitors. Before it can be used in clinical settings, several concerns still need to be explained, such as the more thorough molecular processes of CDK5 in various neurological illnesses and the development of more focused CDK5 inhibitors. Future treatments for ND patients will greatly benefit from those developed with an emphasis on selective techniques.

REFERENCES

1. Chin-Chan M, Navarro-Yepes J, Quintanilla-Vega B. Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. Frontiers in cellular neuroscience, 2015 Apr; 9: 124.
2. Cdk5- Beaudette KN, Lew J, Wang JH. Substrate specificity characterization of a cdc2-like protein kinase purified from bovine brain. Journal of Biological Chemistry, 1993 Oct 5; 268(28): 20825-30.
3. Camins A, Pizarro JG, Folch J. Cyclin-dependent kinases. Brenner’s Encyclopedia of Genetics, 2013; 2: 260-266.
4. Tsai LH, Delalle I, Caviness Jr VS, Chae T, Harlow E. p35 is a neural-specific regulatory subunit of cyclin-dependent kinase 5. Nature, 1994 Sep 29; 371(6496): 419-23.
5. Ko J, Humbert S, Bronson RT, Takahashi S, Kulkarni AB, Li E, Tsai LH. p35 and p39 are essential for cyclin-dependent kinase 5 function during neurodevelopment. Journal of Neuroscience, 2001 Sep 1; 21(17): 6758-71.
6. Kwon YT, Gupta A, Zhou Y, Nikolic M, Tsai LH. Regulation of N-cadherin-mediated adhesion by the p35–Cdk5 kinase. Current Biology, 2000 Apr 1; 10(7): 363-72.
7. Nikolic M, Dudek H, Kwon YT, Ramos YF, Tsai LH. The cdk5/p35 kinase is essential for neurite outgrowth during neuronal differentiation. Genes & development, 1996 Apr 1; 10(7): 816-25.
8. Citri A, Malenka RC. Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology, 2008 Jan; 33(1): 18-41.
9. Huber KM. Synaptic homeostasis: quality vs. quantity. Nature neuroscience, 2018 Jun; 21(6): 774-6.
10. Zeng L, Ao C, Li C, Chen J, Tan J. The role of Cdk5 in neurological disorders. Frontiers in Cellular Neuroscience, 2022 Jul 28; 382.
11. Armstrong RA. Plaques and tangles and the pathogenesis of Alzheimer’s disease. Folia Neuropathologica. 2006 Jan 1; 44(1): 1-1.
12. Patrick GN, Zukerberg L, Nikolic M, de La Monte S, Dikkes P, Tsai LH. Conversion of p35 to p25 deregulates Cdk5 activity and promotes neurodegeneration. Nature, 1999 Dec 9; 402(6762): 615-22.
13. Chang KH, Multani PS, Sun KH, Vincent F, de Pablo Y, Ghosh S, Gupta R, Lee HP, Lee HG, Smith MA, Shah K. Nuclear envelope dispersion triggered by deregulated Cdk5 precedes neuronal death. Molecular biology of the cell. 2011 May 1; 22(9): 1452-62.
14. Lopes JP, Oliveira CR, Agostinho P. Neurodegeneration in an Aβ-induced model of Alzheimer’s disease: the role of Cdk5. Aging cell, 2010 Feb; 9(1): 64-77.
15. Palop JJ, Mucke L. Amyloid-β–induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. Nature neuroscience, 2010 Jul; 13(7): 812-8.
16. Hardy J. Amyloid, the presenilins and Alzheimer's disease. Trends in neurosciences, 1997 May 1; 20(4): 154-9.
17. Iijima KI, Ando K, Takeda S, Satoh Y, Seki T, Itohara S, Greengard P, Kirino Y, Nairn AC, Suzuki T. Neuron-specific phosphorylation of Alzheimer's β-amyloid precursor protein by cyclin-dependent kinase 5. Journal of neurochemistry, 2000 Sep; 75(3): 1085-91.
18. Cruz JC, Kim D, Moy LY, Dobbin MM, Sun X, Bronson RT, Tsai LH. p25/cyclin-dependent kinase 5 induces production and intraneuronal accumulation of amyloid β in vivo. Journal of Neuroscience, 2006 Oct 11; 26(41): 10536-41.

19. Lee MS, Kao SC, Lemere CA, Xia W, Tseng HC, Zhou Y, Neve R, Ahlijanian MK, Tsai LH. APP processing is regulated by cytoplasmic phosphorylation. The Journal of cell biology, 2003 Oct 13; 163(1): 83-95.
20. Wang Y, Mandelkow E. Tau in physiology and pathology. Nature reviews neuroscience, 2016 Jan; 17(1): 22-35.
21. Buee L, Troquier L, Burnouf S, Belarbi K, Van der Jeugd A, Ahmed T, Fernandez-Gomez F, Caillierez R, Grosjean ME, Begard S, Barbot B. From tau phosphorylation to tau aggregation: what about neuronal death?. Biochemical Society Transactions, 2010 Aug 1; 38(4): 967-72.
22. Seo J, Kritskiy O, Watson LA, Barker SJ, Dey D, Raja WK, Lin YT, Ko T, Cho S, Penney J, Silva MC. Inhibition of p25/Cdk5 attenuates tauopathy in mouse and iPSC models of frontotemporal dementia. Journal of Neuroscience, 2017 Oct 11; 37(41): 9917-24.
23. Rao MV, McBrayer MK, Campbell J, Kumar A, Hashim A, Sershen H, Stavrides PH, Ohno M, Hutton M, Nixon RA. Specific calpain inhibition by calpastatin prevents tauopathy and neurodegeneration and restores normal lifespan in tau P301L mice. Journal of Neuroscience, 2014 Jul 9; 34(28): 9222-34.
24. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag AE, Lang AE. Parkinson disease. Nature reviews Disease primers, 2017 Mar 23; 3(1): 1-21.
25. Venda LL, Cragg SJ, Buchman VL, Wade-Martins R. α-Synuclein and dopamine at the crossroads of Parkinson's disease. Trends in neurosciences, 2010 Dec 1; 33(12): 559-68.
26. He F, Qi G, Zhang Q, Cai H, Li T, Li M, Zhang Q, Chen J, Ming J, Tian B, Zhang P. Quantitative phosphoproteomic analysis in alpha-synuclein transgenic mice reveals the involvement of aberrant p25/Cdk5 signaling in early-stage Parkinson's disease. Cellular and Molecular Neurobiology. 2020 Aug; 40: 897-909.
27. Smith PD, Crocker SJ, Jackson-Lewis V, Jordan-Sciutto KL, Hayley S, Mount MP, O'Hare MJ, Callaghan S, Slack RS, Przedborski S, Anisman H. Cyclin-dependent kinase 5 is a mediator of dopaminergic neuron loss in a mouse model of Parkinson's disease. Proceedings of the National Academy of Sciences, 2003 Nov 11; 100(23): 13650-5.
28. Alvira D, Tajes M, Verdaguer E, Acuña-Castroviejo D, Folch J, Camins A, Pallas M. Inhibition of the cdk5/p25 fragment formation may explain the antiapoptotic effects of melatonin in an experimental model of Parkinson's disease. Journal of pineal research, 2006 Apr; 40(3): 251-8.
29. Meredith GE, Totterdell S, Beales M, Meshul CK. Impaired glutamate homeostasis and programmed cell death in a chronic MPTP mouse model of Parkinson's disease. Experimental neurology, 2009 Sep 1; 219(1): 334-40.
30. Apel K, Hirt H. Reactive oxygen species: metabolism, oxidative stress, and signal transduction. Annu. Rev. Plant Biol, 2004 Jun 2; 55: 373-99.
31. Qu D, Rashidian J, Mount MP, Aleyasin H, Parsanejad M, Lira A, Haque E, Zhang Y, Callaghan S, Daigle M, Rousseaux MW. Role of Cdk5-mediated phosphorylation of Prx2 in MPTP toxicity and Parkinson's disease. Neuron, 2007 Jul 5; 55(1): 37-52.
32. Huang E, Qu D, Zhang Y, Venderova K, Haque ME, Rousseaux MW, Slack RS, Woulfe JM, Park DS. The role of Cdk5-mediated apurinic/apyrimidinic endonuclease 1 phosphorylation in neuronal death. Nature cell biology, 2010 Jun; 12(6): 563-71.
33. Dev KK, Hofele K, Barbieri S, Buchman VL, van der Putten H. Part II: α-synuclein and its molecular pathophysiological role in neurodegenerative disease. Neuropharmacology, 2003 Jul 1; 45(1):14-44.
34. Shimura H, Hattori N, Kubo SI, Mizuno Y, Asakawa S, Minoshima S, Shimizu N, Iwai K, Chiba T, Tanaka K, Suzuki T. Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. Nature genetics, 2000 Jul; 25(3): 302-5.
35. Park J, Seo J, Won J, Yeo HG, Ahn YJ, Kim K, Jin YB, Koo BS, Lim KS, Jeong KJ, Kang P. Abnormal mitochondria in a non-human primate model of MPTP-induced Parkinson's disease: Drp1 and CDK5/p25 signaling. Experimental Neurobiology, 2019 Jun; 28(3): 414.
36. Avraham E, Rott R, Liani E, Szargel R, Engelender S. Phosphorylation of Parkin by the cyclin-dependent kinase 5 at the linker region modulates its ubiquitin-ligase activity and aggregation. Journal of Biological Chemistry, 2007 Apr 27; 282(17): 12842-50.
37. Cleveland DW. From Charcot to SOD1: mechanisms of selective motor neuron death in ALS. Neuron, 1999 Nov 1; 24(3): 515-20.
38. Bajaj NP, Al-Sarraj ST, Anderson V, Kibble M, Leigh N, Miller CC. Cyclin-dependent kinase-5 is associated with lipofuscin in motor neurones in amyotrophic lateral sclerosis. Neuroscience letters, 1998 Mar 27; 245(1): 45-8.
39. Bk B, Skuntz S, Prochazkova M, Kesavapany S, Amin ND, Shukla V, Grant P, Kulkarni AB, Pant HC. Overexpression of the Cdk5 inhibitory peptide in motor neurons rescue of amyotrophic lateral sclerosis phenotype in a mouse model. Human Molecular Genetics, 2019 Oct 1; 28(19): 3175-87.
40. Bates GP, Dorsey R, Gusella JF, Hayden MR, Kay C, Leavitt BR, Nance M, Ross CA, Scahill RI, Wetzel R, Wild EJ. Huntington disease. Nature reviews Disease primers, 2015 Apr 23; 1(1): 1-21.
41. McColgan P, Tabrizi SJ. Huntington's disease: a clinical review. European journal of neurology, 2018 Jan; 25(1): 24-34.

42. Wellington CL, Ellerby L, Savill J, Roy S, Leavitt B, Cattaneo E, Hackam A, Sharp A, Thornberry N, Nicholson DW, Bredesen DE. Inhibiting caspase cleavage of huntingtin reduces toxicity and aggregate formation in neuronal and nonneuronal cells. Journal of Biological Chemistry, 2000 Jun 30; 275(26): 19831-8.
43. Liman J, Deeg S, Voigt A, Voßfeldt H, Dohm CP, Karch A, Weishaupt J, Schulz JB, Bähr M, Kermer P. CDK 5 protects from caspase-induced Ataxin-3 cleavage and neurodegeneration. Journal of neurochemistry, 2014 Jun; 129(6): 1013-23.
44. Anne SL, Saudou F, Humbert S. Phosphorylation of huntingtin by cyclin-dependent kinase 5 is induced by DNA damage and regulates wild-type and mutant huntingtin toxicity in neurons. Journal of Neuroscience, 2007 Jul 4; 27(27): 7318-28.
45. Muchowski PJ, Ning K, D'Souza-Schorey C, Fields S. Requirement of an intact microtubule cytoskeleton for aggregation and inclusion body formation by a mutant huntingtin fragment. Proceedings of the National Academy of Sciences, 2002 Jan 22; 99(2): 727-32.
46. Paoletti P, Vila I, Rifé M, Lizcano JM, Alberch J, Ginés S. Dopaminergic and glutamatergic signaling crosstalk in Huntington's disease neurodegeneration: the role of p25/cyclin-dependent kinase 5. Journal of Neuroscience, 2008 Oct 1; 28(40): 10090-101.
47. Luo F, Zhang J, Burke K, Miller RH, Yang Y. The activators of cyclin-dependent kinase 5 p35 and p39 are essential for oligodendrocyte maturation, process formation, and myelination. Journal of Neuroscience, 2016 Mar 9; 36(10): 3024-37.
48. Luo F, Zhang J, Burke K, Romito-DiGiacomo RR, Miller RH, Yang Y. Oligodendrocyte-specific loss of Cdk5 disrupts the architecture of nodes of Ranvier as well as learning and memory. Experimental neurology, 2018 Aug 1; 306: 92-104.
49. Tarricone C, Dhavan R, Peng J, Areces LB, Tsai LH, Musacchio A. Structure and regulation of the CDK5-p25nck5a complex. Molecular cell, 2001 Sep 1; 8(3): 657-69.
50. Zheng YL, Li BS, Amin ND, Albers W, Pant HC. A peptide derived from cyclin-dependent kinase activator (p35) specifically inhibits Cdk5 activity and phosphorylation of tau protein in transfected cells. European journal of biochemistry, 2002 Sep; 269(18): 4427-34.
51. Sundaram JR, Poore CP, Sulaimee NH, Pareek T, Asad AB, Rajkumar R, Cheong WF, Wenk MR, Dawe GS, Chuang KH, Pant HC. Specific inhibition of p25/Cdk5 activity by the Cdk5 inhibitory peptide reduces neurodegeneration in vivo. Journal of Neuroscience, 2013 Jan 2; 33(1): 334-43.
52. Peyressatre M, Prével C, Pellerano M, Morris MC. Targeting cyclin-dependent kinases in human cancers: from small molecules to peptide inhibitors. Cancers, 2015 Jan 23; 7(1): 179-237.