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Review

Role of cyclin-dependent kinase 5 in neurodegenerative disorders

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Alzheimer's disease (AD) is a neurodegenerative confusion associated with dementia. AD is indicated by progressive loss of memory. It is having characteristic evidence of β-amyloid extracellularly and neurofibrillary tangle's development intracellularly. Neurons lose the capability of cell division after they attain full development. Cyclin dependent kinase 5 (Cdk5) is a kinase protein which is neuron specific and plays a vital role in the movement of newly developed neurons. When Cdk5 is dysregulated, then several diseases like AD, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) may occur. The Cdk5 phosphorylation takes place as a result of change of N-methyl-D-aspartate (NMDA) receptor activity and expression, neurotransmitter release, degradation of synaptic proteins, or in-gene expression modulation, which leads to the activation of Cdk5. The activated calpain proteins convert p35 activator of Cdk5 into p25, which causes remarkable activation of the Cdk5. This highly activates Cdk5-p25 complex hyperphosphorylates, the Tau protein, which causes the release of microtubules and gathers as cytoplasmic filaments. This leads to tangle formation that leads to neuronal cell death. In AD brain, the Cdk5 is present in a highly activated form. This review article emphasizes the role of cyclin dependent kinase 5 in AD.

Key words: Alzheimer's disease, β-amyloid plaques, CDK5, neurodegeneration, neurofibrillary tangle.

INTRODUCTION

AD is one of the main causes of dementia. The occurrence of AD increases with age (James et al., 2008; Kang et al., 1987). AD is characterized by the progressive loss of memory related to the decline in language, visuospatial function, estimation and decision. Finally, it leads to major behavioral and functional disability (James et al., 2008; Chung, 2009). AD was originally defined as presenile dementia, but it now appears that the same pathology underlies the dementia irrespective of the age of onset (Rang and Dale, 2007). AD is characterized by a common functional disorder of the brain of humans (Kang et al., 1987). The dementia is mainly due to AD in 60% and vascular reasons (VaD) in 20% (Beghi et al., 2004). In addition to marked neuronal loss, AD is pathologically characterized by deposition of β-amyloid (Aβ) in senile plaques (SPs) extracellularly and development of intracellular NFTs (Garga et al., 2011). The NFTs are primarily composed of hyperphosphorylated tau protein associated with microtubules (Rademakers et al., 2005; Sun et al., 2009; Liu et al., 2006). Normally, the formation of the neurons in the hippocampus of mammals occur throughout life and is vital for the functioning of the brain while in the persons having the disease like AD, PD, and epilepsy, the capability of hippocampus to form neurons is decreased (Albert et al., 2009; Crews et al., 2010). Neurogenesis is the process in which the division of neural stem cells (NSCs) and progenitor cells into daughter cells occur which migrate to other sites and

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Abbreviations: AD, Alzheimer's disease; **NFTs,** neurofibrillary tangles; **sAPP,** secreted amyloid precursor protein; **HD,** Huntington's disease; **ALS,** amyotrophic lateral sclerosis.

gives rise to new neurons (Jessberger et al., 2009). Cdk5 is involved in the movement of newly born neurons of the granule cell layer (GCL). Cdk5 also takes part in exact targeting of dendrites from newly born granule cells (GC) into the molecular layer (ML) of the dentate gyrus (DG). Throughout life the newly born neurons are added to dentate circuitry, with the hippocampal neural progenitor cells NPCs (Albert et al., 2009). Permanent production of new neurons is vital for brain function. The newly formed cells play two distinct roles, firstly the new neurons take part in maintenance of tissue in the olfactory system and secondly they are essential for the development of memory like associative and spatial memory in the hippocampus (Imayoshi et al., 2008). The role of cdk5 in guiding new neurons to their proper place has been discovered, which has increased the understanding of adult neurogenesis, improved understanding of its involvement in cognitive function and brightened the expectations for brain cell therapy (Albert et al., 2009). Also, scarcity in hippocampal neurogenesis has been related with a number of neurological diseases, including AD, epilepsy, major depressions (Albert et al., 2009) and neuropsychiatric illnesses, such as addiction (Hawasli et al., 2009). The abnormal insoluble fibrous proteins are deposited with different proportion inside brain. The localization of fibrous insoluble proteins inside the brain is a characteristic features of several disorders, including AD, PD and Lewy body dementia (LBD) (Mierczak et al., 2011).

PATHOGENESIS OF AD

AD is a progressive and slowly occurring disorder which degrades the central nervous system (CNS) characterrized by impairment of cognitive function and appearance of neuropathological characters, including amyloid plaques. These amyloid plaques are composed of Aβ, NFT and linked to cholinergic neuronal loss in selective brain parts (Nakdooka et al., 2010). The major component of amyloid plaques is Aβ, which is considered as a key molecule in AD pathogenesis (Uetsuki et al., 1999). Inflammation is the third significant pathological feature in AD, apart from NFTs and amyloid plaques (Muyllaert et al., 2008). The oxidative stress hypothesis of AD pathogenesis is based on Aβ peptide, which initiates oxidative stress in both *in vitro* and *in vivo* studies (Sultana et al., 2009). In a normal physiological pathway, amyloid precursor protein (APP) is converted and secreted as amyloid precursor protein (sAPP) which is responsible for the function of growth factor. However, in amyloidogenic pathway, the mutation in APP and presenilin increases the formation of Aβ40 and Aβ42 (Chen et al., 2012). They form aggregates due to mutation in lipid transport protein, that is ApolipoproteinE4 (ApoE4) gene. The production of Aβ40 usually occurs in small amounts, while Aβ42 is produced in higher amounts as a result of the genetic genetic mutations mentioned above (Mann et al., 2011). Both Aβ40 and Aβ42 proteins aggregate to form amyloid plaques, but Aβ42 shows a stronger affinity than Aβ40 to do so, and appears to be the main cause in amyloid formation (Rang et al., 2007). The Aβ40 and Aβ 42 are formed by proteolytic cleavage of a much larger (770 amino acid) APP (Figure 1). The Aβ accumulation is the cause of neurodegeneration, but whether the damage is done by soluble Aβ monomers or by amyloid plaques remains uncertain. Appearance of Alzheimer mutations in transgenic animal results in development of plaque and neurodegeneration (Rang et al., 2007). The aggregation of Aβ40 and Aβ42 also activate the kinase that causes the phosphorylation of Tau protein (Figure 1). Tau, a usual part of neurons, is intracellular microtubules binding protein (Chatterjee et al., 2009). In AD and other tauopathies, phosphorylated tau protein is deposited within the cell as paired helical filaments which have typical microscopic features. After the destruction of cells, these filaments are combined as extracellular neurofibrillary tangles (Crews and Masliah, 2010). It may be possible, but not proven, that the phosphorylation of tau protein is improved by the presence of Aβ plaques. However, it is not sure that hyperphosphorylation and intracellular deposition of tau harm the cells. Although it is known that tau phosphorylation damage fast axonal transport, which depends on microtubules (Rang et al., 2007). Nineteen specific amino acid sequences throughout its 441 amino acids have been recognized in tau, for its phosphorrylation, (Augustinack et al., 2001) associated with paired helical filaments. CDK5 has been considered a main tau kinase that takes part in tau pathology (Alvarez et al., 1999), the other most important tau kinases that takes part in tau pathologies are GSK3α, GSK3β and Casein kinase 1α (CK1α) (Martin et al., 2013).

NEURONAL CELL CYCLE IN PATHOGENESIS OF AD

There are four main successive phases in a eukaryotic cell cycle: G1 phase (first gap), S phase (DNA synthesis), G2 phase (second gap) and M phase (mitosis) (Figure 2). Change between the various phases and consecutive progression through the mitotic cycle is modulated by a group of protein kinases whose activity is essential to this process. The cyclin-dependent kinase (CDKs) requires the binding of their activating partner cyclins; whose levels of appearance vary throughout the cycle. Two important checkpoints (G1/S and G2/M) direct CDKs activity and manage the order and timing of cell-cycle transitions to ensure that DNA replication and chromosome segregation are finished correctly before allowing additional progress throughout the cycle (Currais et al., 2009). Neurons are born throughout the entire life in limited brain areas of mammals, including humans (Jessberger et al., 2009). After the formation of a neuron, it loses the capability for cell division and differentiation, contributing

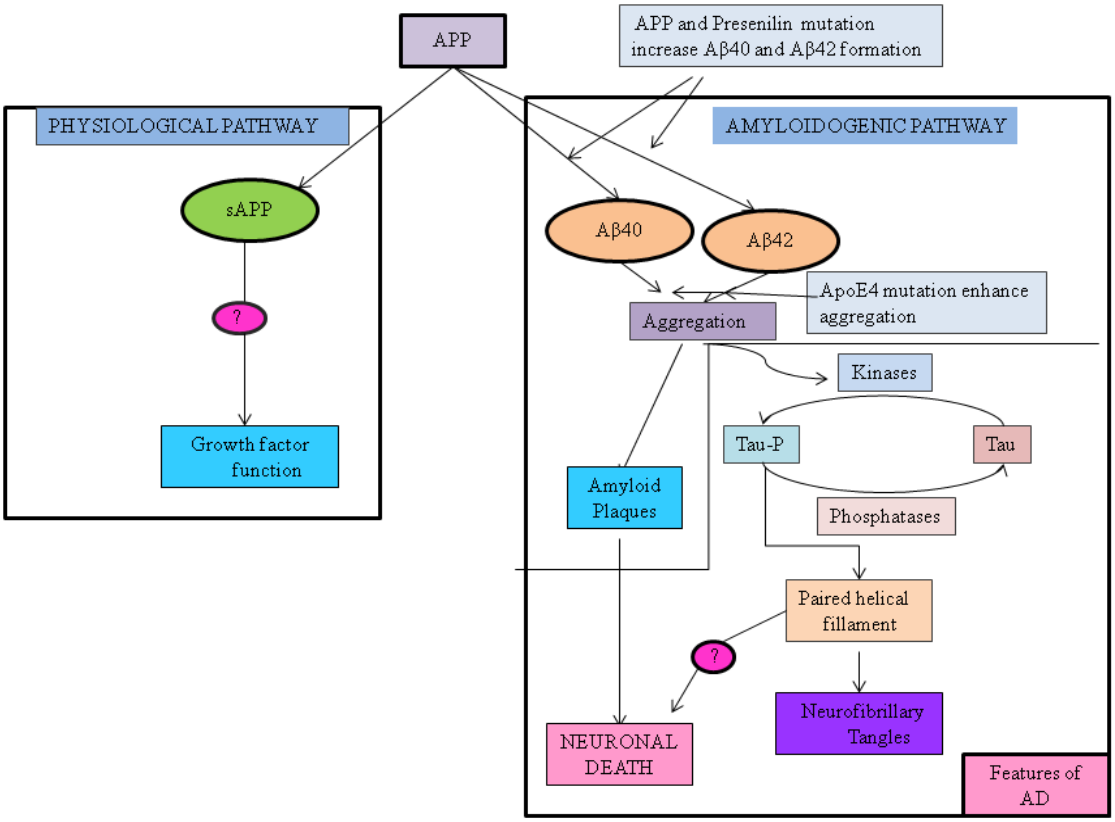

Figure 1. Processing of APP in Pathogenesis of AD. The main 'physiological' path gives rise to sAPP that exerts a number of trophic functions. Cleavage of APP at different places gives rise to Aβ, the major form typically being Aβ40, which is faintly amyloidogenic. Mutations in APP or presenilins raise the amount of APP, which is spoiled via the amyloidogenic pathway, and also raise the proportion changed to the much more powerfully amyloidogenic form Aβ42. Aβ aggregation is occurred by mutations in the apoE4 gene followed by Aggregation of Aβ and forms amyoloid plaque, which causes neuronal death. Aβ aggregation activates the kinase which phosphorylates tau to phosphorylated tau, ultimately form neurofibrillary tangles and cause neuronal death. The figure represents the APP' role in AD
Source: Rang and Dale (1999).

individually to the plasticity of the basic wiring model that defines a neuronal system. The conservation of this pattern is essential for the overall generation and storage of memories, as well as for gaining of other ad-vanced brain skills. Some researcher have reported that neuronal apoptosis is accompanied by the appearance of cell cycle markers. Mainly, cyclins and cyclin-dependent kinases (CDKs) take part in cell cycle machinery (Figure 2). The cell cycle may be up regulated after exposure to severe conditions, like oxidative stress and trophic factor deficiency (Currais et al., 2009; Zhang et al., 2008).

THE CDK FAMILY

The 9 small serine/threonine kinases take part in the formation of Cdk family. They are numbered based on their discovery, that is from Cdk1 to Cdk9. The biological functions of Cdks are many which ranges from mitosis to the regulation of cellular processes (Cardone et al., 2010). Cdks are involved in functions like differentiation, senescence and programmed cell death, via modification of gene transcription. In proliferating cells, the tumor production is mainly linked with Cdk dysregulation (Zafonte et al., 2000). The disappearance or inhibition of neuronal precursors takes place with terminal differentiation (Okano et al., 1993). Normally, in order to be activated, Cdks require connecting with regulatory subunits named cyclins. Although specific Cdks are linked to various phases of the cell cycle, sometimes their activities overlap, depending on the association with different cyclins. Cdk action can also be regulated by two other distinct mechanisms. A set of phosphorylation and dephosphorylation actions make ready Cdks for activation by regulatory subunits, as in the case of the Cdk4/cyclin D1 complex, which are activated only after phosphorylation by the Cdk-activating kinase (CAK).

Additionally, a family of Cdk-inhibitory subunits (CKIs) can bind to it and inactivate the Cdk–cyclin complex (Lopes and Agostinho, 2011).

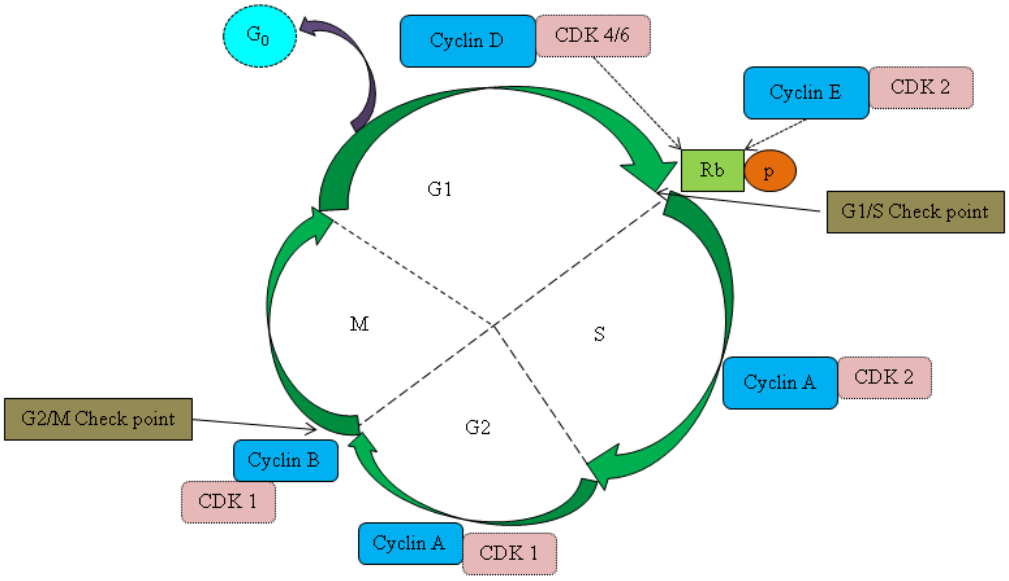

Figure 2. Schematic representation of the eukaryotic cell cycle – Cyclin A-CDK2 phosphorylates a variety of substrates throughout S phase, allowing DNA replication. When S phase completed, DNA replication ceases and then cells enter the G2 phase of the cell cycle. Then CDK2 is replaced by CDK1 that linked with cyclin A and control the phosphorylation of G2 and M phases specific proteins together with cyclin B-CDK1, that appears in late G2 phase and triggers the G2/M transition. Cyclin A is ruined and the cycle is reorganized, re-establishing the condition for mitogenic cues to provoke D-type cyclins for the next cell cycle. In M phase, cells physically divide and originate two separate daughter cells Source: Currais et al. (2009).

CDK5 IN CELL CYCLE REGULATION

Initially, it was said that Cdk5 had no role in the cell cycle (Jessberger et al., 2009). In an abnormal position, the expression of Cdk5 does not encourage development of a cell cycle in yeast or in mammalian cells (Jessberger et al., 2009). It can regulate several cell cycle proteins, mostly, phosphorylating retinoblastoma (Rb) protein, which is an important step in cell cycle exit. The absence of Cdk5 activity in dividing cells in the CNS indicates that it does not have a typical role in cell cycle regulation, which is clearly a significant step in embryonic and also in adult neurogenesis (Jessberger et al., 2009). In the cell cycle, initially the phosphorylation of the Rb protein by Cdk4/cyclin D1 and Cdk6/ cyclin D1-3 and further by Cdk2/cyclin E takes place. A complex is formed by Rb, E2F-1, histone deacetylases (HDAC) between other proteins, at the G1/S check point and blocks' protein transcription and in this way arrest- the cell cycle (Vermeulen et al., 2003). Due to phosphorylation, Rb becomes free from this transcription-blocking complex and allows the transcription of S phase-associated proteins. Sometimes strong stimuli, including excitotoxi- city, oxidative stress, ischemia or DNA damage forces the mature neurons to leave a steady G0 state and re-enter the cell cycle (Bonda et al., 2011; Kim et al., 2009; Klein et al., 2003). Cell cycle re-entry has been observed in different neurodegenerative conditionslike AD, PD and amyotrophic lateral sclerosis (ALS) or stroke (Raina AK et al., 2004; Currais et al., 2009; Wang et al., 2009**)**. In these neurons, the G1 phase is directly related to the re-expression of a cell cycle Cdks, namely Cdk2, 4 and 6. A very important role is played by Rb protein in the unsuccessful cell cycle re-entry. The phosphorylation/ inactivation of Rb causes recycling neurons to rise above the G1/S checkpoint and DNA synthesis will occur. However, these neurons never reach to the M phase and degenerate by apoptosis anywhere between the S and the G2 phases (Lopes and Agostinho, 2011).

LOSS OF NEURONAL CELL CYCLE CONTROL IN AD

Exposure to stress may cause an unsuccessful cell cycle in neurons. AD brain is characterized by the presence of cyclins, CDKs and additional cell cycle proteins (Currais et al., 2009). It is well known that oxidative stress and free radicals play role in pathogenesis of AD. The state of cell cycle is also controlled by free radicals, free radical generators and antioxidant functions. The accumulation of p35 in AD inhibits the cell cycle at G1 phase of cell cycle, which is secondary to oxidative stress. The mitochondria are powerful sources of free radicals and redox dysfunction. Therefore an increase in the number of mitochondria in the same neurons show cell cycle related abnormalities and undergo successive oxidative

harm and cell death in AD. Thus, when the mitochondrial mass is highest, the cell cycle arrest at a point, poses an elevated, chronic, oxidative damage to the cell (Raina et al., 2004).

THE NEUROGENESIS PROCESS

In the adult brain, new neurons are frequently being generated in controlled areas of the mammalian brain, from endogenous pools of neural stem cells during life (Lledo et al., 2006). The process of neurogenesis can be divided into three different phases in the dentate gyrus in mammals. First, neural precursor cells that are located at the border between the hilus, and the granule cell layer (GCL) undergo cell division. Second, newborn cells start to migrate into the GCL and extend neuronal processes. Third, the cells add into the GCL and begin to express the neuronal marker neuron specific enolase (Kuhn et al., 1996). The dentate gyrus (DG) is a precise brain region to which newly formed neurons are added during adulthood (McDonald and Wojtowicz, 2005).

THE CDK5

Cdk5 is a most versatile kinase, and its activity is not stimulated by an associated cyclin but is activated by its specific activators, p35 and p39 (Albert et al., 2009; Valin et al., 2009; Kanungo et al., 2009; Pareek et al., 2010; Changa et al., 2011). Cdk5 is considered as a multi-functional kinase whose activity is limited to the nervous and muscular system (Pareek et al., 2010; Zheng et al., 2010). Cdk5 is a serine/threonine kinase which is governed by proline (Pareek et al., 2007; Hawasli et al., 2009; Takahashi et al., 2010; Hisanaga et al., 2010; Arif et al., 2011). Unlike the other kinases, the cell cycle is not directly controlled with this serine–threonine kinase. Cdk5 can phosphorylate the Rb proteins, which have a major intervenient role in cell cycle development. Like the other members of this group, Cdk5 requires to combine with a regulatory subunit for its activation. Although, Cdk5 does not combine with cyclins (Zhang et al., 2012), it combines with the neuron specific activators p35 and p39 which are structurally similar to cyclins (Dhavan et al., 2002; Crews et al., 2011). Further, Cdk5 does not require any additional phosphorylation for its activation. However, the phosphorylation at tyrosine 15 (Tyr15) by enzyme tyrosine kinases-Src can increase the action of this protein (Cancino et al., 2011). The enzymatic activity of Cdk5 is more important in the CNS, since the appearance of this kinase and its activators is maximum in postmitotic neurons (Lopes and Agostinho, 2011; Kusakawa et al., 2000). Cdk5 activators p35 and p39 are degraded easily. The levels of these proteins are governed by their synthesis and degradation, and the appearance of p35 is exposed to be induced by an extracellular stimulus. Neurotrophic factors, like nerve growth factor (NGF) also cause an enhancement of p35 appearance. The phosphorylation condition of p35 as well affects the membrane association of the Cdk5/p35 complex. The communication of this complex with the membrane is a possible regulatory method of Cdk5. It has been shown that when the Cdk5/p35 complex binds with membrane; it becomes inactive, while the complex in the free form in the cytoplasm is the active form (Lopes and Agostinho, 2011). Cdk5 appearance was found mainly in the brain, and Cdk5 activity, found only in the nervous tissues (Ohshima et al., 1996). Cdk5-null mutants indicate a more accurate disturbance in the cerebral cortex, cerebellum and hippocampus (Ko et al., 2001).

ROLE OF CDK5 IN NEUROBIOLOGICAL PROCESS

Normally, the Cdk5 is essential for proper movement of nerve cells, synapse formation, and survival of neuronal cells. However, the severe neurodegenerative disorders like AD, ALS, PD and HD are mainly linked with hyper-activation of Cdk5 (Pareek et al., 2010; Shukla et al., 2011). Cdk5 takes part in different neurobiological processes; such as homeostatic synaptic plasticity, dopamine signaling, neuronal degeneration, and learning and memory. Cdk5 has also been concerned in normal adult neurophysiology, and its inhibition in the hippocampus leads to marked disturbance in associative learning and memory (Albert et al., 2009). Cdk5 plays a significant role in distinct aspects of cortical growth, which includes neuronal migration, neurite development, and axonal path finding. Different from other Cdks which are major regulators of cell-cycle progression, Cdk5 mainly causes phosphorylation of tau proteins in neurons. If the Cdk5 gene is deleted from neurons of the forebrain, by expression of cre-recombinase (Type 1 Topoisomerase), then this approach leads to generation of viable mice with decreased expression of Cdk5 in the forebrain. The expression of cre-recombinase is governed by the supporter of the CaMKII (calcium/calmodulin dependent kinase II) (Takahashi et al., 2010). It can be suggested that when neuronal Cdk5 from the developing forebrain is removed, it may result in the complex neurological loss, growth retardation, and premature mortality in mice (Takahashi et al., 2010). Recently, Cdk5-p35 has been linked with the initiation of disease in nonneuronal lineages for example malignant alteration in cancer; stimulation of inflammatory pain, and other pain mediated disorders. Cdk5–p35 activity has been, reported in human leukemic cell and supposed to play a role in monocytic differentiation (Pareek et al., 2010). The Cdk5–p35 complex is important for activation of T cell and for the initiation of experimental autoimmune encephalomyelitis (EAE) (Pareek et al., 2010). In the absence of Cdk5 mice show perinatal lethality due to having abnormal positioning of neurons in the brain (Hisanaga and

(Hisanaga and Endo, 2010). Cdk5 phosphorylation of tau inhibits its binding to microtubules and promotes microtubule disassembly. The Cdk5 phosphorylates tau at two major sites like Thr231 and Ser262, which are followed by GSK-3 that prevents binding of tau to MT (Sengupta et al., 2006). The surface expression of NMDA receptors (NMDARs) regulated by Cdk5, are the most important group of ionotropic glutamate receptors, which contains various heteromeric complexes like NR1, NR2, and NR3 subunits. These NMDARs are also concerned in development of neurons, learning and memory, synaptic plasticity and addiction in addition to psychiatric and neurodegenerative disorders (Zhang et al., 2008; Li et al., 2001).

CDK5 IN NEURODEGENERATION

CDK5 dysregulation

Dysregulation of this Cdk5 is responsible for the neurodegenerative processes of several diseases, like AD, PD, prion-related encephalopathies (PRE), amyotrophic lateral sclerosis (ALS) or acute neuronal injury, which are produced by ischemia or stroke (Figure 3). The activity of Cdk5 increases in various neurodegenerative disorders like AD, PD, PRE, ALS, etc. (Lopes et al., 2009).

Role of Cdk5 in AD

AD brain is identified by three main markers, that is amyloid plaque deposition, neurofibrillary tangle production and severe selective neuronal loss. Cdk5 act as an attractive candidate for preventing Aβ toxicity, tau pathology and neurodegeneration. In AD affected brains of human, the activity of Cdk5 increases appreciably as compared with same age control brains of human (Tandon et al.,2003). In AD brains, the levels of p25 and activated calpain are increased (Tandon et al., 2003; Muyllaert et al., 2008).

Cdk5 in Aβ generation

All the mutations which cause AD are situated either in the APP gene or in the genes encoding presenilins 1 (PS1) and 2 (PS2). PS1 and PS2 are the two proteins which are part of the γ-secretase (γ-sec) complex in which one of the secretases is responsible for APP cleavage to Aβ. Further it is also proved that Aβ can activate Cdk5 dysregulation (Lopes and Agostinho, 2011). *In vivo*, study of Aβ established that the production of Aβ involves enhancing intraneuronal calcium levels, that mainly cause calpain activation and enhancement of Cdk5 activity because of the cleavage of p35 to p25 (Dolan and Johnson, 2010).

Cdk5 in Tau pathology

Tau is associated with proteins known as microtubule associated proteins (MAP) so tau is referred as a member of MAP family (Sergeant et al., 2004). The main function of tau proteins are binding and stabilization of the cellular microtubular network (Mandelkow and Mandelkow, 1995). So, tau is necessary to vital processes like axonal transport (Torroja et al., 1999), cytoskeletal organization or mitotic division (Preuss and Mandelkow, 1998). Phosphorylation of tau protein is controlled by numerous kinases, mainly glycogen synthase kinase 3β (GSK-3β), cAMP-dependent protein kinase (PKA), Cdk5 and c-Abelson (c-Abl) kinase or Abl-related gene (Arg) kinase (Martin et al., 2013). GSK-3β is referred as tau kinase I and Cdk5 is referred as tau kinase II (Liu et al., 2006). Tau is a phosphoprotein and the fetal brain tau is more heavily phosphorylated than adult brain tau (Goedert et al., 1993). It is confirmed that any change in hyper phosphorylation of tau is critical to neurofibrillary degeneration (Liu et al., 2006). Tau hyper phosphorylation may be associated with decrease in phosphatase activity while the tau phosphorylation is associated with an increase in protein kinase activity (Buee et al., 2000). GSK-3α, GSK-3β and Cdk-5 are the members of the MAP kinase family and GSK-3β-mediates the phosphorylation of tau and reduce its affinity for microtubules (Wagner et al., 1996).

Role of CDK5 in Parkinson disease

PD is the second most common neurodegenerative disease, which is due to loss of dopamine neurons (Cookson, 2009). The dysfunctioning of the dopaminergic and glutamatergic neurotransmitter systems results in Parkinson's disease. In the striatum, CDK5 decreases the postsynaptic release of dopamine. CDK5 inhibitors increase evoked dopamine release. The glutamatergic transmission is also controlled by the presynaptic action of CDK5. In fact, CDK5 inhibition increases the activity and phosphorylation of *N*-methyl-D-aspartate (NMDA) receptors. On other hand, these effects are reduced by dopamine D1 receptor antagonist. Inhibitors of CDK5 enhance dopaminergic transmission at both presynaptic and postsynaptic locations. The ability of CDK5 inhibitors to prevent degeneration of dopaminergic neurons, indicate that the compounds of this class could potentially be used as a new treatment for disorders connected with dopamine deficiency, such as Parkinson's disease (Chergui et al., 2004).

ROLE OF CDK5 IN AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease, an adult-onset disease. It leads to selective loss

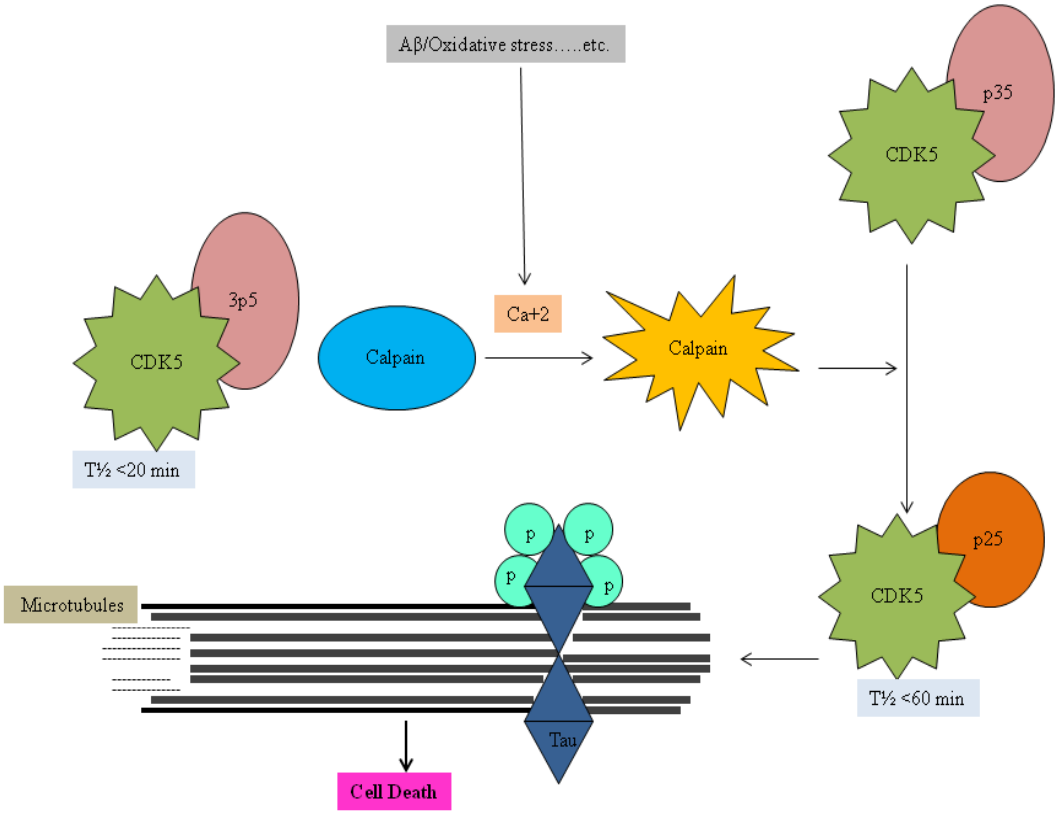

Figure 3. Dysregulation of CDK5 through activation of Calpains and hyperphosphorylation of Tau protein.The activator proteins like p35 and p39 are broken in the process of Cdk5 dysregulation by calpains. Calpains are the group of Ca^{2+} activated cytosolic proteases. The production of p25 and p29 occurs through the cleavage of p35 and p39 by calpains, respectively. These reduced Cdk5 activators show different features from their original precursors. The half-life of p35 and p39 are significantly shorter, around the 3-fold than p25 and p29 and the binding affinity of these newly formed activators to the kinase is stronger than previous activators. Finally the Cdk5 activity increases as compared to Cdk5/p35 (or p39) .The formation of Cdk5/p25 complex are self regulated. After dysregulation, Cdk5 hyperphosphorylates the cytoskeleton protein tau, then this cause the release of tau protein from the microtubules and gathering in the form of cytoplasmic filaments and tangles occurs (Martin et al., 2013; Zhang et al., 2008).

of motor neurons in the spinal cord, brainstem and cerebral cortex, ultimately resulting in paralysis and death over 1 to five year time course. Approximately, 10% of ALS patients are familial cases, 20% of which are caused by missense mutations in the enzyme Cu/Zn superoxide dismutase 1 (SOD1) (Patzke and Tsai, 2002). Nguyen et al. (2001) developed a mechanism to explain the degeneration of motor neurons caused by mutant SOD1. For this purpose $SOD1^{G37R}$, mice were used; they observed myslocalization and hyperactivation of the Ser/Thr kinase cdk5. The increase in the p25/p35 ratio in $SOD1^{G37R}$ mice indicates an up regulation of calpain activity, suggestive of elevated Ca^{2+} levels in the affected cells. Motor neurons expressing mutant SOD1 are more susceptible to glutamate-mediated cell death than are wild-type neurons (Patzke and Tsai, 2002; Nguyen et al., 2001). The increased Cdk5 activity in $SOD1^{G37R}$ mice was associated with hyper phosphorylation of tau and NF proteins, which are Cdk5 cytoskeletal substrates. The hyperphosphorylation of these proteins has been associated with Alzheimer's disease (Nguyen et al., 2001).

ACTIVATION OF CDK-5

The activation of Cdk5 occurs with tunable activation threshold-p25 (TAT-p25) which is Temporal Activator of Cdk5 in Primary Neurons. TAT-p25 is formed by fusion of TAT sequence with p25, which cause temporal activation of Cdk5, which is not dependent on other stimuli (Sun et al., 2008).

CDK5 IN DIFFERENT PATHWAY OF NEURODEGENERATION

The Cdk5 dysregulation depends on the disturbance of

intracellular calcium homeostasis. Normally, disturbance of intracellular calcium homeostasis is caused by an extreme activation of ionotropic glutamate receptors (Lopes and Agostinho, 2011). The glutamate receptor over activation occurs due to various triggering stimuli. Over activation of Cdk5 results in too many phosphorylation of the cytoskeleton protein tau, which correlates with the synaptic loss and production of neurofibrillary tangles in AD, ultimate results are neuronal death (Kerokoski et al., 2002). Cdk5 also phosphorylates α-synuclein and parkin, two proteins, which take part in the pathogenesis of PD (Avraham et al., 2007; Duka et al., 2006). Cdk5 furthermore, regulates an event that causes synaptic dysfunction via the phosphorylation of Postsynaptic density-95 (PSD-95) which results in the internalization and degradation of NMDA receptors (Roselli et al., 2005). Caspase-3 activation also results in neuronal death (Samuel et al., 2007). The capacity of the cells to bear oxidative stress is also affected by Cdk5 dysregulation, which is confirmed by the inactivation of the peroxidase Prx2, via Cdk5 phosphorylation, in PD and ALS (Shukla et al., 2011, Rashidian et al., 2009). All these events clearly indicate that Cdk5 dysregulation is a major step in the neurodegeneration pathways of various neurological disorders (Shukla et al., 2011).

RECENT ADVANCES AND FUTURE ASPECTS OF THE CDK5 IN AD

Cdk5 is an important target for CNS disease. It may become possible that by inhibition of Cdk5, the phosphorrylation of tau and formation of neurofibrillary tangles is prevented in both AD and tauopathies. There are various potent Cdk5 chemical inhibitors discovered, but they mostly compete with the ATP binding site which may cause lack of specificity in other Cdks and other ATP dependent kinases (Glicksman et al., 2007). It is assumed that specific inhibitors may inhibit the interaction of tau and Cdk5, which binds to a site other than ATP binding site (Glicksman et al., 2007). The calpain also convert the Cdk5-p39 to Cdk5-p25, which is more active than Cdk5-p39 (Zhang et al., 2008). Therefore, it may be possible to treat the AD by inhibition of calpains through calpain inhibitors, which inhibit the change of Cdk5-p39 to Cdk5-p25. Very recently three drugs have been developed by two companies, i.e.; cysteyl-leucyl-argininal (Trade name: Neurodur) from CepTor Corp., aminocarnityl-glutaryl-leucyl-argininal (Trade name: Myodur) from CepTor Corp., in the USA and BDA- 410 from Mitsubishi-Tokyo Pharmaceuticals in Japan (Rosa et al., 2002).

DISADVANTAGES OF CDK5 ACTIVITY

It is found that the overactive Cdk5 cause neuronal death under oxidative stress from a variety of sources, such as amyloid-β-peptide and the increase of intra-neuronal calcium level. It is due to p25, which is a more powerful activator of Cdk5 as compared to p35 and causes Cdk5 over activation with neuronal apoptosis (Lin, 2009).

CONCLUSION

In this review, it is concluded that the Cdk5 plays a vital role in the brain development through its involvement in the processes of neuronal migration. This review not only focused on development of AD, PD, and ALS as a result of Cdk5 dysregulation, but also framed the role of Cdk5 in other neurodegenerative pathologies, such as prion encephalopathies or PD. Overactivation and myslocalization of Cdk5 due to Ca^{2+} induced calpain activation mediates tau hyperphosphorylation and apoptotic neuronal death. In different neurodegenerative disorders, it may be assumed that Cdk5 can be a superior pharmacological target to prevent these pathologies. The normal activity of Cdk5 is essential to provide neuropro- tection. It includes cognition and memory, neuronal survival, neuronal development and migration, etc. For these purposes, two main strategies have been used, first is direct inhibition by using Cdk5 inhibitors to prevent over activation of Cdk5 and second is indirect action by preventing the excessive production of the pathogenesis-associated activator p25 by using the calpain inhibitors.

Therefore, finally we assume that over activation of Cdk5 and calpains enhance neurodegeneration and can become a major cause of memory loss. However, the inhibition of Cdk5 overactivation and calpains through specific inhibitors prevent neurodegeneration and help in memory development.

REFERENCES

Albert T, Saxena M, Lelievre V (2009). CDK5 the “pathfinder” for new born neurons in adult hippocampus. Cell Adh. Migr. 3(4):319-321.

Alvarez A, Toro R, Caceres A (1999). Inhibition of tau phosphorylating protein kinase cdk5 prevents L-amyloid-induced neuronal death. FEBS Lett. 459:421-426.

Arif A, Jia J, Moodt RA (2011). Phosphorylation of glutamyl-prolyl tRNA synthetase by cyclin-dependent kinase 5 dictates transcript selective translational control. PNAS 108(4):1415-1420.

Augustinack JC, Schneider A, Mandelkow EM, Hyman BT (2001). Specific tau phosphorylation sites correlate with severity of neuronal cytopathology in Alzheimer’s disease. Acta Neuropathol. 103:26–35.

Avraham E, Rott R, Liani E (2007). Phosphorylation of Parkin by the Cyclin-dependent Kinase 5 at the Linker Region Modulates Its Ubiquitin-Ligase Activity and Aggregation. J. Biol. Chem. 282(17):12842–12850.

Beghi E, Logroscino G, Korczyn A (2004). Alzheimer’s disease and other dementias. Chapter 18, pp. 285-296.

Bonda DJ, Lee H, Kudo W (2011). Pathological implications of cell cycle re-entry in Alzheimer disease. Expert Rev. Mol. Med. 12:1-11.

Buee L, Bussiere T, Scherrer VB (2000). Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. Brain Res. Rev. 33:95-130.

Cancino G I, Arce K P, Castro P U (2011). c-Abl tyrosine kinase modulates *tau* pathology and Cdk5 phosphorylation in AD transgenic mice. Neurobiol. Aging 32(7):1249–1261.

Cardone A, Hassan SA, Albers RW (2010). Structural and dynamic determinants of legand binding and regulation of Cyclin-dependent Kinase 5 by pathological activator p25 and inhibitory peptide CIP. J.

Mol. Biol. 401(3):478-492.
Changa K, Multania P, Suna K (2011). Nuclear envelope dispersion triggered by deregulated Cdk5 precedes neuronal death. Mol. Biol. Cell. 22(9): 1452–1462.
Chatterjee S, Sang TK, Lawless GM (2009). Dissociation of tau toxicity and phosphorylation: role of GSK-3b, MARK and Cdk5 in a Drosophila model. Hum. Mol. Gen. 18(1):164-177.
Chen WT, Hong CJ (2012). Amyloid-Beta (Ab) D7H Mutation Increases Oligomeric Ab42 and Alters Properties of Ab-Zinc/Copper Assemblies. PLoS One 7(4):1-12.
Chergui K, Svenningsson P, Greengard P (2004). Cyclin-dependent kinase 5 regulates dopaminergic and glutamatergic transmission in the striatum. PNAS 101(7):2191–2196.
Chung SH (2009). Aberrant phosphorylation in the pathogenesis of Alzheimer's disease. BMB Rep. 42:467-474.
Cookson MR (2009). α-Synuclein and neuronal cell death. Mol. Neurodegener. 4(9):1-14.
Crews L, Masliah E (2010). Molecular mechanisms of neurodegeneration in Alzheimer's disease. Hum. Mol. Gen. 19: R12-R20.
Crews L, Patrick C, Adame A (2011). Modulation of aberrant CDK5 signaling rescues impaired neurogenesis in models of Alzheimer's disease. Cell Death Dis. 2(120):1-13.
Currais A, Hortobágyi T, Soriano S (2009). The neuronal cell cycle as a mechanism of pathogenesis in Alzheimer's disease. Aging 1(4):363-369.
Dhavan R, Greer PL, Morabito MA (2002). The Cyclin-Dependent Kinase 5 Activators p35 and p39 Interact with the α-Subunit of $Ca2^{+}$/Calmodulin-Dependent Protein Kinase II and α-Actinin-1 in a Calcium-Dependent Manner. J. Neurosci. 22(18):7879–7891.
Dolan PJ, Johnson G (2010). The role of tau kinases in Alzheimer's. Curr. Opin. Drug Discov. Dev. 13(5):595-603.
Duka T, Rusnak M, Drolet R E (2006). Alpha-Synuclein induces hyperphosphorylation of *Tau* in the MPTP model of Parkinsonism. FASEB J. 20:2302-2312.
Garga S, Timma T, Mandelkow EM (2011). Cleavage of Tau by calpain in Alzheimer's disease: the quest for the toxic 17 kD fragment. Neurobiol. Aging 32:1-14.
Glicksman MA, Cuny GD, Liu M (2007). New approaches to the discovery of cdk5 inhibitors. Curr. Alzheimer Res. 5:247-249.
Goedert M, Jakes R, Crowther RA (1993). The abnormal phosphorylation of tau protein at Ser-202 in Alzheimer disease recapitulates phosphorylation during development. Proc. Nat. Acad. Sci. 90:5066-5070.
Hawasli AH, Koovakkattu D, Hayashi K (2009). Regulation of Hippocampal and Behavioral Excitability by Cyclin-Dependent Kinase 5. PLOS ONE. 4(6):1-13.
Hisanaga S, Endo R (2010). Regulation and role of cyclin-dependent kinase activity in neuronal survival and death. J. Neurochem. 115:1309-1321.
Imayoshi I, Sakamoto M, Ohtsuka T (2008). Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. Nat. Neurosci. 11:1153-61.
James MR, Leonel DL, Timothi GK (2008). A text book of clinical Pharmacology and Therapeutics. Alzheimer's disease. Hodder Arnold, Hachette Livre. Britain UK. p 131.
Jessberger S, Gage FH, Eisch AJ (2009). Making a Neuron: Cdk5 in Embryonic and Adult Neurogenesis. Trends Neurosci. 32(11):575-582.
Kang J, Lemaire HG, Unterbeck A (1987). The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Nature 733-736.
Kanungo J, Zheng Y, Amin ND (2009). Specific Inhibition of cyclin dependent Kinase 5 Activity Induces Motor Neuron Development in vivo. Biochem. Biophys. Res. Commun. 386(1):263-267.
Kerokoski P, Suuronen T, Salminen A (2002). Cleavage of the cyclin-dependent kinase 5 activator p35 to p25 does not induce tau hyper-phosphorylation. Biochem. Biophys. Res. Commun. 298: 693–698.
Kim D, Tsai LH (2009). Linking Cell Cycle Reentry and DNA Damage in Neurodegeneration. International Symposium on Olfaction and Taste: Ann. NY Acad. Sci. 1170:674–679.
Klein JA, Ackerman SL (2003). Oxidative stress, cell cycle, and neurodegeneration. J. Clin. Invest. 111:785–793.
Ko J, Humbert S, Bronson RT (2001). p35 and p39 Are Essential for Cyclin-Dependent Kinase 5 Function during Neurodevelopment. J. Neurosci. 21(17):6758-6771.
Kuhn HG, Anson HD, Gage FH (1996). Neurogenesis in the dentate gyrus of the Adult Rat: Age-Related Decrease of Neuronal Progenitor Proliferation. J. Neurosci. 76(6):2027-2033.
Kusakawa G, Saito T, Onuki R (2000). Calpain-dependent Proteolytic Cleavage of the p35 Cyclin-dependent Kinase 5 Activator to p25. J. Biol. Chem. 275(22):17166-17172.
Li BS, Sun MK, Zhang L (2001). Regulation of NMDA receptors by cyclin-dependent kinase-5. PNAS 98(22):12742-12747.
Lledo PM, Alonso M, Grubb ML (2006). Adult neurogenesis and functional plasticity in neuronal circuits. Nat. Neurosci. 7:179-193.
Lin H (2009). The Versatile Roles of Cyclin-Dependent Kinase 5 in Human Diseases. Adaptive Med. 1(1):22-25.
Liu F, Liang Z, Shi J (2006). PKA modulates GSK-3β- and cdk5-catalyzed phosphorylation of tau in site- and kinase-specific manners. FEBS Lett. 580(26):6269-6274.
Lopes JP, Agostinho P (2011). Cdk5: Multitasking between physiological and pathological conditions. Prog. Neurobiol. 94:49-63.
Lopes JP, Oliveira CR, Agostinho P (2009). Cdk5 acts as a mediator of neuronal cell cycle re entry triggered by amyloid-b and prion peptides. Cell Cycle. 8(1):97-104.
Mandelkow E, Mandelkow EM (1995). Microtubules and microtubule-associated proteins. CO-CellBiol. 7:72-81.
Mann DMA, Brown SMP, Takeuchi A, Iwatsubo T (2001). Amyloid Angiopathy and Variability in Amyloid b Deposition Is Determined by Mutation Position in Presenilin-1-Linked Alzheimer's Disease. AJP 158(6):2165-2175.
Martin L, Latypova X, Wilson CM (2013). Tau protein kinases: Involvement in Alzheimer's disease. Ageing Res. Rev. 12:289-309.
McDonald HY, Wojtowicz JM (2005). Dynamics of neurogenesis in the dentate gyrus of adult rats. Neurosci. Lett. 385:70–75.
Mierczak AK, Czapski GA, Adamczyk A (2011). A novel mechanism of non-Aβ component of Alzheimer's disease amyloid (NAC) neurotoxicity. Interplay between p53 protein and cyclin-dependent kinase 5 (Cdk5). Neurochem. Int. 58:206-214.
Muyllaert D, Terwel D, Kremer A (2008). Neurodegeneration and Neuroinflammation in cdk5/ p25-Inducible Mice A Model for Hippocampal Sclerosis and Neocortical Degeneration. Am. J. Pathol. 172(2):470-486.
Nakdooka W, Khongsombata O, Taepavarapruka P (2010). The effects of Tabernaemontana divaricata root extract on amyloid β-peptide 25–35 peptides induced cognitive deficits in mice. J. Ethnopharmacol. 130:122-126.
Nguyen MD, Lariviere RC, and Julien JP (2001) Deregulation of Cdk5 in a mouse model of ALS: toxicity alleviated by perikaryal neurofilament inclusions. Neuron 30:135–147.
Ohshima T, Ward JM, Huht C (1996). Targeted disruption of the cyclin-dependent kinase 5 gene resultsin abnormal corticogenesis, neuronal pathology and perinatal death. Neurobiology 93:11173-11178.
Okano HJ, Pfaff DW, Gibbs RB (1993). RB and Cdc2 expression in brain: correlations with 3H-thymidine incorporation and neurogenesis. J. Neurosci. 13:2930–2938.
Pareek TK, Keller J, Kesavapany S (2007). Cyclin dependent kinase 5 modulates nociceptive signaling through direct phosphorylation of transient receptor potential vanilloid 1. PNAS 104(2):660-665.
Pareek TK, Lam E, Zheng X (2010). Cyclin-dependent kinase 5 activity is required for T cell activation and induction of experimental autoimmune encephalomyelitis. J. Exp. Med. 207(11):2507-2519.
Patzke H, Tsai LH (2002). Cdk5 sinks into ALS. Trends Neurosci. 25(1):8-10.
Preuss U, Mandelkow EM (1998). Mitotic phosphorylation of tau protein in neuronal cell lines resembles phosphorylation in Alzheimer's disease. Eur. J. Cell Biol. 76:176-184.
Rademakers R, Sleegers K, Theuns J (2005). Association of cyclin-dependent kinase 5 and neuronal activators p35 and p39 complex in early-onset Alzheimer's disease. Neurobiol. Aging 26:1145-1151.
Raina AK, Zhu X, Smith MA (2004). Alzheimer's disease and the cell cycle. Acta Neurobiol. Exp. 64:107-112.
Rang HP, Dale MM, Ritter JM (2007). Rang and Dale's Pharmacology,

6th ed. Neurodegenerative diseases. Churchill Livingstone, Elsevier. pp. 514-517.
Rashidian J, Rousseaux MW, Venderova K (2009). Essential Role of Cytoplasmic cdk5 and Prx2 in Multiple Ischemic Injury Models, *in vivo*. J. Neurosci. 29(40):12497–12505.
Rosa GD, Odrljin T, Nixon RA (2002). Calpain Inhibitors: A Treatment for Alzheimer's Disease. J. Mol. Neurosci. 19:135–141.
Roselli F, Tirard M, Lu J (2005). Soluble β-Amyloid$_{1–40}$ Induces NMDA-Dependent Degradation of Postsynaptic Density-95 at Glutamatergic Synapses. J. Neurosci. 25(48):11061–11070.
Samuel MA, Morrey JD, Diamond MS (2007). Caspase 3-Dependent Cell Death of Neurons Contributes to the Pathogenesis of West Nile Virus Encephalitis. J. Virol. 81(6):2614–2623.
Sengupta A, Novak M, Iqbal IG, Iqbal K (2006). Regulation of Phosphorylation of Tau by Cyclin-dependent Kinase 5 and Glycogen Synthase Kinase-3 at Substrate Level. FEBS Lett. 580(25):5925-5933.
Sergeant N, Delacourte A, Buee L (2004). Tau protein as a differential biomarker of tauopathies. Biochim. Biophys. Acta. 1739:179–197.
Shukla V, Mishra SK, Pant HC (2011). Oxidative Stress in Neurodegeneration. Adv. Pharmacol. Sci. 1-13.
Sultana R, Perluigi M, Butterfield DA (2009). Oxidatively modified proteins in Alzheimer's disease (AD), mild cognitive impairment and animal models of AD: role of Abeta in pathogenesis. Acta Neuropathol. 118:131-150.
Sun KH, Lee H, Smith MA (2009). Direct and Indirect Roles of Cyclin-dependent Kinase 5 as an Upstream Regulator in the c-Jun NH2-Terminal Kinase Cascade: Relevance to Neurotoxic Insults in Alzheimer's disease. Mol. Biol. Cell. 20:4611-4619.
Sun K, Pablo Y, Vincent F (2008). Novel Genetic Tools Reveal Cdk5's Major Role in Golgi Fragmentation in Alzheimer's disease. Mol. Biol. Cell. 19:3052-3069.
Takahashi S, Ohshima T, Hirasawa M (2010). Conditional Deletion of Neuronal Cyclin-Dependent Kinase 5 in Developing Forebrain Results in Microglial Activation and Neurodegeneration. Am. J. Pathol. 176(1):320-329.
Tandon A, Yu Haung, Wang L (2003). Brain levels of CDK5 activator p25 are not increased in Alzheimer's or other neurodegenerative diseases with neurofibrillary tangles. J. Neurochem. 86:572–581.
Torroja L, Chu H, Kotovsky I (1999). Neuronal over expression of APPL, the *Drosophila* homologue of the amyloid precursor protein (APP) disrupts axonal transport. Curr. Biol. 9(9):489-492.
Uetsuki T, Takemoto K, Nishimura I (1999). Activation of Neuronal Caspase-3 by Intracellular Accumulation of Wild-Type Alzheimer Amyloid Precursor Protein. J. Neurosci. 19(16):6955–6964.
Valin A, Cook JD, Ross S (2009). Sp1 and Sp3 regulate transcription of the cyclin-dependent kinase 5 regulatory subunit 2 (p39) promoters in neuronal cells. Biochim. Biophys. Acta 1789(3):204-211.
Vermeulen K, Van Bockstaele DR, Berneman Zwi N (2003). The cell cycle: a review of regulation, deregulation and therapeutic targets in cancer. Cell Prolif. 36:131–149.
Wagner U, Utton M, Gallo J M (1996). Cellular phosphorylation of tau by GSK-3b influences tau binding to microtubules and microtubule organization. J. Cell Sci. 109:1537-1543.
Wang W, Bu B, Xie M (2009). Neural cell cycle dysregulation and central nervous system diseases. Progr. Neurobiol. 89:1–17.
Zafonte BT, Hulit J, Amanatullah DF (2000). Cell-cycle dysregulation in breast cancer: breast cancer therapies targeting the Cell cycle. Frontiers Biosci. 5:938-961.
Zhang J, Cicero SA, Wang L (2008). Nuclear localization of Cdk5 is a key Determinant in the postmitotic state of neurons. Proc. Natl. Acad. Sci. USA 105(25):8772-77.
Zhang J, Li H, Zhou T (2012). Cdk5 levels oscillate during the neuronal cell cycle: Cdh1 ubiquitination triggers proteosome-dependent degradation during S-phase. J. Biol. Chem. 287:25985-25994.
Zhang S, Edelmann L, Liu J (2008). Cdk5 Regulates the Phosphorylation of Tyrosine 1472 NR2B and the Surface Expression of NMDA Receptors. J. Neurosci. 28(2):415-424.
Zheng Y, Li B, Rudrabhatla P (2010). Phosphorylation of p27Kip1 at Thr187 by Cyclin-dependent Kinase 5 Modulates Neural Stem Cell Differentiation. Mol. Biol. Cell. 21:3601-3614.