

Review Article

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Synaptic roles of cyclin-dependent kinase 5 & its implications in epilepsy

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There is an urgent need to understand the molecular mechanisms underlying epilepsy to find novel prognostic/diagnostic biomarkers to prevent epilepsy patients at risk. Cyclin-dependent kinase 5 (CDK5) is involved in multiple neuronal functions and plays a crucial role in maintaining homeostatic synaptic plasticity by regulating intracellular signalling cascades at synapses. CDK5 deregulation is shown to be associated with various neurodegenerative diseases such as Alzheimer's disease. The association between chronic loss of CDK5 and seizures has been reported in animal models of epilepsy. Genetic expression of CDK5 at transcriptome level has been shown to be abnormal in intractable epilepsy. In this review various possible mechanisms by which deregulated CDK5 may alter synaptic transmission and possibly lead to epileptogenesis have been discussed. Further, CDK5 has been proposed as a potential biomarker as well as a pharmacological target for developing treatments for epilepsy.

Key words Cyclin-dependent kinase 5 - epilepsy - epileptogenesis - neurodegenerative diseases - pharmacoresistant - seizures - synaptic plasticity

Introduction

Imbalance between excitation and inhibition is a hallmark of epileptogenesis. Although numerous studies have reported association between abnormal synaptic transmission and epileptogenesis, yet the molecular mechanisms underlying genesis of seizures in patients with epilepsy, especially with drug-resistant epilepsy (DRE), is still unclear. It is estimated that in about 30-40 per cent of epilepsy patients, treatment with antiepileptic drug (AED) alone will not result in complete seizure control¹ (Fig. 1). Most patients with DRE can be diagnosed early in their presentation

after they failed treatment with two AEDs². DRE patients have an increased risk of mortality and a poor social life. They undergo various investigations such as video electroencephalography (EEG) to confirm the diagnosis of epilepsy and magnetic resonance imaging (MRI) study to identify a potential surgical lesion. Functional imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) localize cerebral dysfunction by identifying disturbances in an individual's metabolism or blood flow. A recently emerged non-invasive technique,

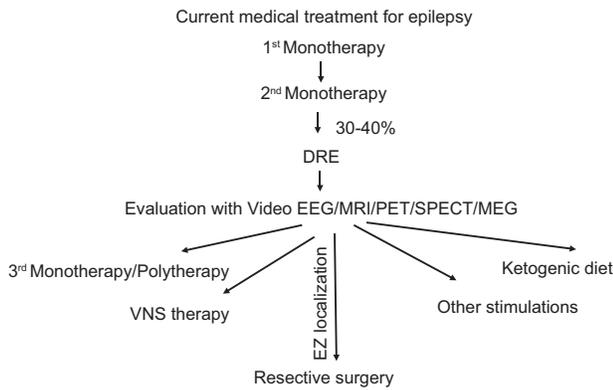


Fig. 1. Schematic representation of the current treatment sequence for drug-resistant epilepsy (DRE) patients. About 30-40 per cent of the epilepsy patients whose seizures do not successfully respond to two different monotherapies with antiepileptic drug are considered as DRE patients. Various investigative techniques [video electroencephalography (EEG)/magnetic resonance imaging (MRI)/positron emission tomography (PET)/single photon emission computed tomography (SPECT)/magnetoencephalography (MEG)] are used to confirm the diagnosis for accurate treatment and also for localization of the epileptogenic zone (EZ) in resective surgery. Treatments for DRE patients includes vagus nerve stimulation (VNS) or responsive cortical stimulations or ketogenic diets and resective surgery.

magnetoencephalography (MEG), is very potent in localizing the irritative zone in lesional and non-lesional epilepsy surgery patients as well as in functional mapping of eloquent (sensory, motor and language) cortex for surgical planning³ (Fig. 1). Other options are suggested for patients who are either not suitable candidates for surgery or those who continue to have seizures even after surgery. These include treatment trials with other AEDs appropriate for their epilepsy syndrome and/or vagus nerve stimulation (VNS) or responsive cortical stimulations or ketogenic diets⁴. With these treatments, the chances of seizure remission are not high, but certainly, the reductions in seizure frequency and improvement in the quality of life are possible in most of the patients. Patients with localization-related DRE undergo resective surgical therapy and have greater chances of achieving surgical freedom as compared to those receiving medical treatment for DRE³. Intraoperative co-registration of MRI, PET, and electrocorticography (ECoG) provides better objective localization of the epileptogenic foci. ECoG provides useful information for the prediction of surgical success in surgically remediable epilepsy³. Despite using combination of all available invasive and non-invasive modalities, the epileptogenic zone cannot be fully defined, and in more than 30 per cent of cases, the patients are not benefited, mostly due to inability to precisely localize the epileptogenic foci⁵. Thus, the

challenge is to understand the molecular mechanisms of epileptogenesis, which will aid in identifying potential diagnostic biomarkers as well as novel therapeutic targets of epilepsy. The tissues resected during epilepsy surgery are the ideal model systems for studying the process of epileptogenesis, and only a complementary and multi-disciplinary approach will lead to a novel biomarker.

To understand the molecular basis of DRE, whole-genome transcriptomic analysis approach has been used to identify genes involved in the pathophysiology of DRE^{5,6}. Several potential candidate genes, mostly linked to, inflammation and innate immunity, synaptic transmission and network modulation, were found to be modulated. Various kinases involved in phosphorylation of microtubule-associated proteins (MAPs) including glycogen synthase kinase-3 beta (GSK3 β), cyclin-dependent kinase 5 (CDK5), MAP kinase family members (ERK, P38) and casein kinase 2 (alpha 1 polypeptide) were abnormally expressed. MAP kinase, CDK5 and casein kinase 2 were shown to be deregulated in both DRE patients and animal models of epilepsy⁶.

Deregulation of the mechanisms inhibiting excitatory synaptic transmission or promoting the mechanisms that facilitate excitation can lead to epileptogenesis. Seizure-induced alterations of synaptic plasticity including neuronal sprouting, reorganization of synapse, neurogenesis and gliosis can result in the development of abnormal neural network⁵. This will lead to a loss of the inhibitory effect of endogenous antiepileptic system. These changes will further prevent the traditional AEDs from reaching their targets and gradually leading to the development of DRE. Many studies have shown that neuropeptides such as somatostatin (SST), neuropeptide Y (NPY), galanin and nociceptin/orphanin FQ (N/OFQ) have antiepileptic activity and thus act as endogenous antiepileptic agents⁷. Due to high-frequency stimulation (as observed in seizure), interneuronal peptides are released from interneurons causing inhibition of synaptic transmission. In addition, adenosinergic system is reported to have an endogenous antiepileptic function by virtue of its anticonvulsant action⁸. It is important to understand the processes through which the neuronal activities are synchronized which in turn lead to generation of seizures. Modulation of synaptic plasticity will lead to modulation of neurotransmission which is crucial for memory formation as well as higher cognition in the central nervous system (CNS). Various kinases including a serine/threonine kinase CDK5 regulate

synaptic plasticity by modulating synaptic composition of postsynaptic density (PSD) by phosphorylation of various synaptic proteins⁹. However, the regulation of neural plasticity by CDK5 is still not clearly understood. Studies with transgenic animals have associated CDK5 with an increasing number of higher brain functions and neurodegenerative diseases such as drug addiction, spatial learning, memory formation and Alzheimer's disease¹⁰. Mirza *et al*¹¹ published an integrated analysis of several array-based studies on the transcriptional profiling of human epilepsy where they have identified CDK5 signalling pathway as one of the top canonical pathways modulated in epilepsy strongly supporting the role of CDK5-mediated signalling in epilepsy. This review is mainly focussed on the role of CDK5 in synaptic transmission and suggests that altered CDK5 functions in epilepsy patients may affect the synaptic transmission, thereby contributing to the process of epileptogenesis.

Role of cyclin-dependent kinase 5 (CDK5) in neuronal function

CDK5 is a unique multi-functional proline-directed serine/threonine kinase which is activated by two non-cyclin activators, p35 and p39¹². CDK5 shares 60 per cent homology to cell division cycle protein 2¹³. Initially, CDK5 was shown to have no role in the cell cycle, but recently, it has been shown to regulate several cell cycle proteins. Most of these phosphorylate retinoblastoma proteins which play a crucial role in cell cycle exit. CDK5/p35 complex bound to the membrane is inactive, whereas the unbound complex in the cytoplasm is the active form. CDK5 localizes both in the cytoplasm and nucleus¹⁴. Myristoylated p35 or p39 leads to the recruitment of CDK5 to cellular membranes in the cell soma and the dendrites¹⁵. Cleavage of p35 into p25 affects the activity, localization and interactive network of CDK5¹⁶. Maximal enzymatic activity of CDK5 and its activators is found in the postmitotic neurons in the CNS. CDK5-null mutants indicated precise modulations in the cerebral cortex, cerebellum and hippocampal regions¹⁷. It is implicated in multiple neuronal functions, including neuronal survival and migration, neurite outgrowth, synaptic vesicle cycle, synaptic transmission and plasticity¹⁸⁻⁷⁴ (Fig. 2). Furthermore, CDK5 along with its cofactors has been shown to regulate neuronal excitability. Large numbers of synaptic proteins have been reported as CDK5 substrates. CDK5 inhibition has been shown to unmask the silent synapses by potentiating the release of neurotransmitters in neurons⁷⁵.

CDK5 is linked to the neuronal death in Alzheimer's and Parkinson's disease and plays an important role in the pathophysiology of these neurodegenerative diseases^{76,77}. Understanding of the precise role of CDK5 modulation of neurotransmission affecting synaptic dysfunction associated with these neurological disorders may open new avenues for novel therapeutics.

Role of cyclin-dependent kinase 5 (CDK5) in abnormal synaptic transmission associated with epilepsy

CDK5 function in synaptic vesicle cycle

Numerous studies have identified defects in the synaptic vesicle cycle as one of the reasons for the abnormal release. CDK5 phosphorylates various

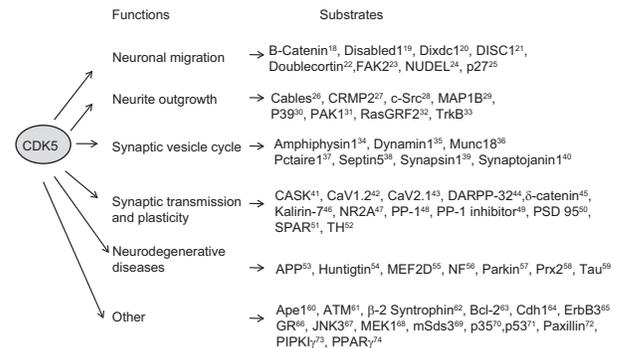


Fig. 2. Major identified cyclin-dependent kinase 5 (CDK5) substrates. Substrates are categorized based on their functions. Superscript numerals denote reference numbers.

DISC1, disrupted in schizophrenia 1 protein; FAK2, flagellar adenylate kinase; NUDEL, nuclear distribution protein nude-1; P27, cyclin-dependent kinase inhibitor 1B; CRMP2, dihydropyrimidinase like 2; c-Src, proto-oncogene tyrosine-protein kinase; MAP1B, microtubule-associated protein 1B; P39, cyclin-dependent kinase 5, regulatory subunit 2; PAK1, serine/threonine-protein kinase; RasGRF2, ras-specific guanine nucleotide-releasing factor 2; TrkB, BDNF/NT-3 growth factors receptor; CASK, peripheral plasma membrane protein; CaV1.2, voltage-dependent L-type calcium channel subunit alpha; CaV2.1, voltage-gated calcium channel alpha 1A subunit; DARPP-32, dopamine- and cAMP-regulated neuronal phosphoprotein; NR2A, glutamate receptor, ionotropic, N-methyl D-aspartate; PP-1, protein phosphatase 1; PSD95, postsynaptic density protein 95; SPAR, surfactant protein A binding protein; TH, tyrosine 3-monooxygenase; APP, amyloid beta A4 protein; MEF2D, myocyte-specific enhancer factor 2D; NF, neurofibromin; Prx2, peroxidase; Tau, Microtubule-associated protein tau; Ape1, DNA-(apurinic or apyrimidinic site) lyase; ATM, serine-protein kinase ATM; Bcl-2, apoptosis regulator Bcl-2; Cdh1, cadherin-1; ErbB3, receptor tyrosine-protein kinase erbB-3; GR, glucocorticoid receptor; JNK3, mitogen-activated protein kinase 10; MEK1, dual specificity mitogen-activated protein kinase 1; mSds3, component of the functional mSin3/HDAC corepressor complex; p35, cyclin dependent kinase 5 regulatory subunit 1; PIPKI- γ , phosphatidylinositol-4-phosphate 5-kinase type 1 gamma; PPAR- γ , peroxisome proliferator-activated receptor gamma.

substrates such as synapsin I, Munc18, Sept5, calcium/calmodulin-dependent serine protein kinase 3, P/Q subtype voltage-dependent calcium channel and Pctaire1, a CDK-related kinase, and plays an important role in synaptic vesicle cycle^{36,43,78}. CDK5 regulates clathrin-mediated endocytosis by phosphorylating various substrates including amphiphysin I, dynamin I, phosphatidylinositol-4-phosphate 5-kinase type I gamma (PIPKI γ) and synaptojanin 1, a PI(4,5)P2 phosphatase⁷⁹. There is evidence showing implication of CDK5 in the inhibition of dopamine (DA) release in the striatum⁸⁰. Collectively, CDK5 has been proposed to inhibit the neurotransmitter release. Deregulation of CDK5 may result in excessive release of neurotransmitter leading to epileptogenesis.

Modulation of neurotransmitter receptors at glutamatergic synapses

There are reports showing alterations in the excitatory (glutamatergic) and inhibitory (GABAergic) synaptic transmission in resected surgery zone from epilepsy patients. Involvement of CDK5 in modulating glutamatergic neurotransmission has been reported⁸⁰. Putkonen *et al*⁸¹ reported kainic acid (KA) induced activation of CDK5 in cultured hippocampal neurons as well as *in vivo* in the hippocampus. GluR6/7 and PSD95 were found to be decreased after KA treatment in the hippocampal neurons. Further, CDK5 inhibition using roscovitine, silencing RNA or dominant-negative CDK5 constructs was able to counteract the decreases in the levels of these proteins in cultured hippocampal neurons. This study provided crucial information on the role of CDK5 in modulating synaptic plasticity and excitotoxicity after KA treatment. CDK5 has been shown to influence the clustering of the PSD95 complexes and regulate trafficking of metabotropic GluRs and N-methyl-d-aspartate receptor (NMDAR) subunits⁵⁰. CDK5 enhances NMDA-mediated currents in hippocampal neurons by phosphorylating the NMDAR subunit 2A (NR2A). CDK5 also facilitates calpain-mediated degradation of the NR2B subunit of NMDAR. A study by Putkonen *et al*⁸¹ reported the role of CDK5 in regulating the α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor (AMPA) subunit GluR2-mediated synaptic activity by phosphorylating D-catenin⁸¹. CDK5 primes polo-like kinase 2 (Plk2) which in turn affects the recruitment and degradation of RapGAP (Spine Associated RapGAP) that interacts with PSD95^{82,83}. CDK5 is needed to maintain homeostasis during increased excitotoxicity by negative regulation of the synaptic

activity. CDK5 knockout (KO) may affect calpain-mediated p25 generation, leading to disruption of the normal homeostatic mechanisms preventing seizures⁸³. CDK5 also regulates acetylcholine receptor (AChR) clustering and plays a role in the neuromuscular junction (NMJ) development. NMJ phenotype of CDK5-KO mice demonstrated that the bandwidth of AChR endplate was enlarged in CDK5/2 diaphragm¹¹.

CDK5 also modulates expression of neurotransmitter receptors at the synapse. CDK5 upregulates GABA_A receptors transcription in the CNS neurons by phosphorylating the transcription factor signal transducer and activator of transcription 3 (STAT3). CDK5-mediated regulation of myocyte-enhancing factor 2 (MEF2) is linked with neuronal death and also in the death of dopaminergic neurons in animal model of Parkinson's disease. Activity-dependent regulation of MEF2 activity also appears to affect the number of excitatory synapses¹¹. Thus, deregulation of CDK5 affecting neurotransmitter receptor transcription at the synapse may be another possible mechanism leading to epileptogenesis.

Dopaminergic signalling

DA-mediated modulation of intracellular signalling pathways has been shown to be involved in long-term epileptogenesis. CDK5-mediated phosphorylation of the DA synthesis catalytic enzyme, tyrosine hydroxylase, regulates its stability in the presynaptic terminals⁵². In postsynaptic neurons, CDK5 regulates cyclic-AMP-regulated phosphoprotein-32kD [dopamine- and cyclic-AMP regulated phosphoprotein-32Kd (DARPP-32)] which is a crucial molecule in DA signalling⁷⁹. CDK5 antagonizes dopamine 1 receptor (D1R)-mediated protein kinase A (PKA) signalling by phosphorylating T75 residue of DARPP-32 and turning it into a PKA inhibitor and protein phosphatase 1 (PP1) activator. In contrast, phosphorylation of DARPP-32 at T34 residue through D1R-PKA signalling inhibits PP1 which in turn promotes phosphorylation activity. Collectively, CDK5 plays an important role in maintaining dopaminergic homeostasis. Various studies report crosstalk between the CDK5- and GSK3 β -mediated signalling pathways. CDK5 inhibits GSK3 β by either inhibiting phosphatases or activating protein kinase B (PKB) or Akt through erythroblastosis oncogene B (ErbB) signalling (Fig. 3). Modulation of Akt/GSK3 signalling by DA receptors has been shown to influence NMDA receptor-mediated synaptic plasticity⁸⁴. CDK5 has been shown to down-regulate D2R surface expression,

thereby reducing D2R Gi-coupling and downstream cAMP pathway⁸⁵. The expression of CDK5 is shown to be regulated by Δ FosB which in turn is activated by DA signalling⁸⁶ (Fig. 3). D1R-mediated increased CDK5 expression may further deregulate D1R signalling modulating various downstream targets leading to epileptogenesis. Two major intracellular signalling pathways (PKA/ERK/Fos/Jun and Akt/GSK3 β /mTOR), downstream of D1R and D2R, might play an important role in regulating seizure-induced neuronal death, gliosis and epileptogenesis⁸⁷. CDK5 shows crosstalk with both these pathways. PKA, Akt,

GSK3 β and related signalling pathways are implicated in the pathophysiology of various neurological as well as psychiatric disorders.

Role of CDK5 in epileptogenesis

Epileptogenesis is the process of generation of chronic spontaneous seizures driven by neuronal insults. The process of epileptogenesis includes multiple events related to cell death, cell survival and functions related to synaptic plasticity including neuronal death, neuronal migration, axonal sprouting, synaptic reorganization and gliosis. Therefore, there are many possibilities of abnormalities in different signalling mechanisms that could be responsible for the development of epilepsy. Here, we have mainly discussed the possible role of CDK5-mediated abnormal synaptic transmission in epileptogenesis. CDK5 is a versatile kinase with multiple neuronal functions.

There are several ways through which CDK5 can lead to epileptogenesis by modulating synaptic transmission. This section summarizes how deregulation of CDK5 can lead to epileptogenesis and also discusses the potential of CDK5 as a therapeutic target. CDK5 is a key player in regulating homeostatic plasticity which is crucial for stabilizing the activity of neurons and the neuronal circuits. Homeostatic plasticity may play a role in the prevention of epilepsy by balancing the excitatory and inhibitory neurotransmission⁵¹. Glutamatergic activation of ionotropic receptors mediated excitability is regulated by DA and metabotropic glutamate receptors (Fig. 3). Deregulated CDK5 may alter dopaminergic homeostasis in conditions of increased levels of glutamate causing excitotoxic damage. Glutamatergic activation of NMDAR and AMPAR causes increase in intracellular Ca²⁺ concentration, leading to increased CDK5 activity which in turn results in aberrations in neuronal excitability. There are reports showing such aberrant excitatory feedback circuit and spontaneous seizure in p352/2 mice¹¹, reflecting that CDK5 may also contribute to seizure activity. In normal conditions, CDK5 may inhibit abnormal epileptiform activity whereas induce it under conditions of stress or brain insults that result in non-physiological Ca²⁺ influx (Fig. 4).

CDK5 has been implicated in modulating long-term potentiation (LTP) and long-term depression (LTD)⁸⁸. LTP and LTD are long-lasting alterations in the synaptic strength facilitated by modulations in synaptic activity.

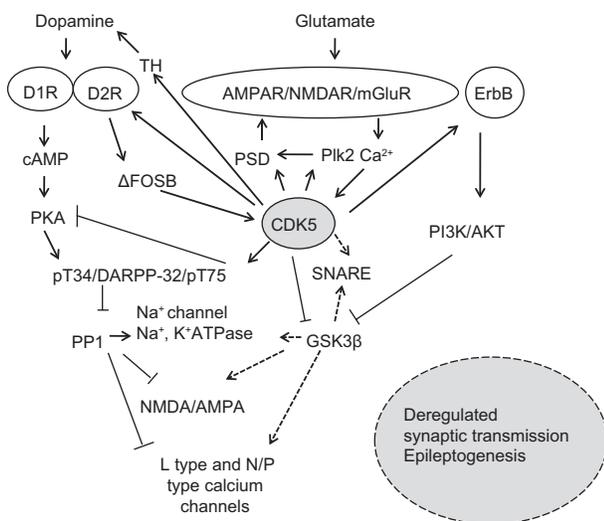


Fig. 3. Hypothesized model of the pathways/substrates regulated by cyclin-dependent kinase 5 (CDK5) in dopamine and glutamate signalling. Depicted are postsynaptic dopamine/PKA/Thr34-DARPP-32, glutamate/CDK5/Thr75-DARPP-32, CDK5/Plk2/PSD/NMDA/AMPA/mGluR, and CDK5/GSK3 β /PI3K/AKT, Δ FosB/CDK5 signalling cascades. CDK5 might play important role in regulating synaptic transmission by either directly influencing glutamate signaling through NMDAR/AMPA/mGluR via PSD and Plk2, or maintaining dopaminergic homeostasis via DARPP-32 phosphorylation and Akt/GSK3 signalling. DA signaling might further regulate CDK5 expression via Δ FosB. Deregulation of these pathways by CDK5 may alter synaptic transmission that may further lead to epileptogenesis. D1R, dopamine receptor D1; D2R, dopamine receptor D2; TH, tyrosine 3-monooxygenase; cAMP, cyclic adenosine 3',5'-monophosphate; PKA, cAMP-dependent protein kinase; pT34 and pT75, phospho theronine 34 and 75; DARPP-32, dopamine- and cAMP-regulated neuronal phosphoprotein; FOSB, fosB proto-oncogene, AP-1, transcription factor subunit; GSK3 β , glycogen synthase kinase-3 beta; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor; PI3K, phosphatidylinositol 3-kinase; AKT, serine/threonine kinase; ErbB, epidermal growth factor receptor; NMDAR, glutamate receptor ionotropic, -methyl D-aspartate; AMPAR, 2-Amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid glutamate receptor; mGluR, metabotropic glutamate receptor; PSD, post synaptic density; PIK2, phosphatidylinositol 3-kinase 2.

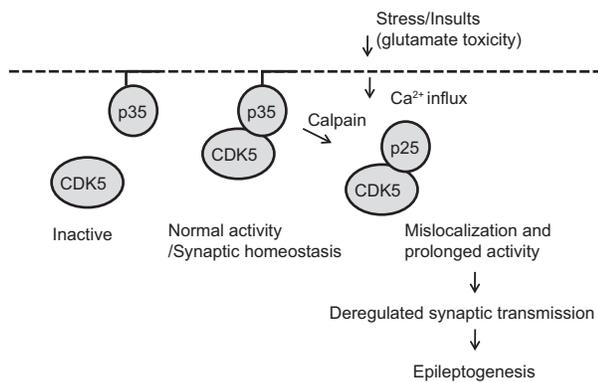


Fig. 4. Diagram showing cyclin-dependent kinase 5 (CDK5) maintaining synaptic homeostasis in a normal state or promoting epileptogenic activity under conditions of stress/brain insults that result in non-physiological Ca^{2+} influx.

Usually, high-frequency stimulations lead to LTP which facilitates synaptic efficacy for longer durations. On the other hand, low-frequency stimulation-induced LTD facilitates decrease in synaptic efficacy lasting for hours to months. In patients with temporal lobe epilepsy, a marked reduction of LTP was observed in the epileptic focus of hippocampus⁸⁹. One study has reported the role of CDK5 inhibition in LTP induction, and the proposed mechanisms include activation of DA and NMDAR, L-type Ca^{2+} channels, PKA signalling and neurotransmitter release⁹⁰. Activation of NR2B and NR2A subunits containing NMDARs is shown to be associated with LTD and LTP, respectively. CDK5 can modulate both LTP and LTD by regulating various subunits of NMDARs. It inhibits clustering of NMDAR (calpain-mediated degradation of the NR2B NMDAR) and AMPAR (D-catenin-dependent localization of GluR2), resulting in excitability^{45,91}. In rat CA1 hippocampal neurons, CDK5 was shown to enhance NMDA-mediated currents by phosphorylation of the NR2A subunits. Therefore, CDK5 inhibition can block both inductions of LTP as well as NMDA-evoked currents⁴⁷.

Cyclin-dependent kinase 5 (CDK5) as a potential prognostic/diagnostic biomarker

A biomarker is defined as highly sensitive, specific and easily measurable molecular alterations of a normal or pathologic condition in a biological media such as human tissues, cells or fluids⁹². Epilepsy is multifactorial and different epilepsy syndromes are associated with different pathophysiology. Therefore, it is not possible to have a single common set of biomarkers for all epilepsies; however, there is a possibility of

limited commonalities for all of the DREs. Molecules associated with epileptogenesis and ictogenesis have potential to serve as biomarkers. These biomarkers can predict the development as well as the progression of an epileptic condition. These could also identify the epileptogenic focus by measuring the presence and severity of tissue capable of generating spontaneous seizures. These biomarkers can also be used to develop animal models for cost-effective screening of potential anti-epileptogenic and anti-seizure drugs and devices⁹³. The present epileptic biomarkers include imaging and electrophysiological measurements⁹³. We still do not have any definitive molecular or cellular biomarker for epilepsy, and till now, there are no biomarkers for DRE. The molecular mechanisms underlying DRE that differentiate it from other forms of epilepsy are still not clear and this could be contributing in part for the lack of biomarkers for DRE. The proposed mechanisms for DRE include inappropriate drug target as there are numerous receptors and ion channels with multiple isoforms involved in neuronal excitability, poor drug distribution due to overexpression of multidrug efflux genes and finally the homeostatic mechanisms that lead to the development of tolerance.

Deregulated CDK5 may lead to disrupted synaptic drive by modulating either LTP or LTD and may serve as a novel biomarker as well as a pharmacological target for treatment of epilepsy. It has been shown that long-term, but not acute loss of CDK5 activity can lead to increased Mg^{2+} -sensitive potentials⁸³. This will further lower the threshold for epileptiform activity and seizures. Thus, CDK5 is proposed to be activated as a homeostatic mechanism to attenuate epileptiform activity⁸³. Owing to the numerous neuronal functions, crosstalk with multiple intracellular signalling pathways, regulation of homeostatic plasticity and capability to increase the threshold for seizures CDK5 may play a crucial role in generating epileptiform activity and seizures and thus may serve as potential biomarkers of epileptogenesis and ictogenesis.

Although expression level analysis reveals modulation of CDK5 signalling in epilepsy, further validation studies for the role of this candidate gene or its interacting partners in epilepsy are so far conducted only in animal models of epilepsy^{6,11,81}. As none of the animal models for epilepsy could replicate the aetiopathological conditions in humans, it is important to do such studies in human brain tissues to conceptualize its role in epileptogenesis in human. Gene expression analysis in resected brain tissues from

human shows alterations in the mRNA levels of CDK5, and studies in animal models show modulations in the phosphorylated CDK5 (p-CDK5) levels^{11,81}.

Currently, anticonvulsant therapeutics is used to target either voltage-gated Na⁺ channels or T-type Ca²⁺ channels. These drugs are effective in only 70 per cent of adults suffering from recurrent seizures and are also associated with undesired side effects. In rat hippocampus, inhibition of CDK5 using a small molecule inhibitor resulted in significant increase in synaptic transmission⁴³. Another study proposed that the inhibitor targeted calcium channels as the small molecule inhibitor potentiated calcium currents even in the absence of p35, a major regulator for CDK5 in the brain⁹⁴. However, it has also been suggested that the residual activity could also be driven by p39, another regulator of CDK5³⁰. Numerous CDK5 inhibitors have been shown to be neuroprotective in both neuronal cell cultures and animal models. Roscovitine was shown to suppress ischaemia-induced tau hyperphosphorylation in animal stroke models⁹⁵. Olomoucine, another molecule with similar structure significantly reduced ischaemia-induced reactive astrogliosis⁹⁶. An inhibitory peptide which specifically targets the deregulated CDK5/p25 complex⁹⁷, was shown to provide neuroprotective effects in nerve cell cultures again supporting the notion that CDK5 could be a potential drug target in various neurological disorders.

Conclusions

CDK5 has significant implications in regulating synaptic plasticity, and as alterations of synaptic plasticity lead to epileptogenesis, it is proposed that deregulated CDK5-mediated altered synaptic transmission may lead to epileptogenesis. Targeting CDK5 and the downstream pathways might prove beneficial for the treatment of neurodegeneration and hyperexcitability observed in epilepsy. In addition, being a key regulator of homeostatic plasticity, CDK5 may play a crucial role in the pathophysiology of DRE and may also have the potential to serve as a prognostic/diagnostic biomarker of DRE.

Conflicts of Interest: None.

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