Roles of PI3K/AKT/PTEN Pathway in the Pathogenesis of Parkinson’s Disease and the Neuropsychiatric Symptoms

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Authors’ contributions

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ABSTRACT

Parkinson's disease is a neurodegenerative disorder associated with loss of dopaminergic neurons in substantianigra caused by severe neuro-degeneration, which is the second most common neurodegenerative disorder after Alzheimer's disease. Parkinson's disease has a high prevalence of psychiatric comorbidity including depression. The neuropsychiatric symptoms are common in Parkinson's disease and may precede onset of motor symptoms. Increasing interest is often addressed to the selective targeting of some of metabotropic glutamate receptors that inhibit the transmitter release at synapses in the basal ganglia. The metabotropic glutamate receptors may be coupled to the phosphatidylinositol-3-kinase (PI3K), AKT, and PTEN pathways, which play a central role in cell survival. A better understanding of the molecular connections in the PI3K pathways could uncover new targets for drug development in Parkinson's disease.

Keywords: Parkinson’s disease; depression; mGlu receptors; PI3K; AKT; PTEN.

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ABBREVIATIONS

GAP: GTPase-activating protein; GSK-3: Glycogen synthase kinase 3; HtrA2: high temperature requirement protein A2; MARK2: Microtubule affinity-regulating kinase 2; mGlu: metabotropic glutamate; mTOR: mammalian target of rapamycin; PARL: presenilin-associated rhomboid-like; PD: Parkinson’s disease; PDK1: phosphoinositide-dependent kinase 1; PDZ: PSD-95, DLG1, and ZO-1; PEST: proline, glutamic acid, serine and threonine; PH: plekstrin homology; PINK1: PTEN-induced kinase-1, phosphatase and tensin homologue-induced kinase 1; PIP2: phosphatidylinositol 4,5-biphosphate; PIP3: phosphatidylinositol 3,4,5-triphosphate; PTEN: phosphatase and tensin homolog; TRAP1: tumor necrosis factor receptor-associated protein-1; TSC1: tuberous sclerosis complex 1; ZnPP: Zinc protoporphyrin IX.

1. INTRODUCTION

Parkinson’s disease (PD) is a movement disorder represented by the production of tremor, rigidity, and bradykinesia [1]. In addition, PD patients also suffer from non-motor symptoms such as cognitive impairment and depression [2]. PD is the most common neurodegenerative disorder after Alzheimer’s disease, which affects the central nervous system [3,4]. The major disturbances in PD patients are due to the loss of dopaminergic neurons in the substantia nigra which results in the alterations of striatal synaptic transmission in the basal ganglia [5]. Metabotropic glutamate (mGlu) receptors have been shown to play a key role in the striatal function both in physiological and in pathological conditions affecting this neuronal area [6]. The dopaminergic neurons are susceptible to inflammations and oxidative stresses due to the environment of the dopamine biosynthetic pathways and the low mitochondrial reserve compared to other neuronal populations [7,8]. Furthermore, advances in the treatment of Parkinson’s disease have led to improvement in many of the motor symptoms of the disease, but often on the cost of neuropsychiatric side-effects, which include psychosis, dopamine dysregulation syndrome, and mood disorders. Current treatments for PD are designed at addressing motor symptoms, but there is no therapy focused on modifying the progression of the disease. So, treatment strategies have been restricted.

The mGlu receptors have received much attention, driven by a belief in the potential of these modulatory glutamate receptors as drug targets. Some evidence emphasizes the role of certain mGlu receptors in reversing motor deficits in PD and dopamine-deficient animals [9-11]. The mGlu receptors modulate synaptic transmission in the central nervous system and represent promising therapeutic targets for symptomatic treatment of PD. The mGlu receptors also regulate PI3K and AKT signaling pathway (Fig. 1), which plays a crucial role in the mechanisms of PD [12]. Activation of the mGlu receptors/AKT signaling pathway seems to play a crucial role in the mechanisms of PD pathogenesis. This paper provides a concise overview of the potential cellular functions of the mGlu receptors and the AKT signaling, and the molecular interplay in the processes underlying the neurodegenerative disorders.
Fig. 1. There are three groups of mGlu receptors, which are associated with heterotrimeric G proteins. Implication of the initial molecular mechanisms that regulate the mGlu receptors signaling is shown. Note that some critical molecules have been omitted for clarity.

2. EXPRESSION AND CHARACTERISTICS OF METABOTROPIC GLUTAMATE RECEPTORS

The mGlu receptors are a part of a family of eight G-protein-coupled receptors classified into three groups (I, II and III, Fig. 1) according to their sequence homologies, second messenger coupling, and ligand selectivity [13]. Group II and III mGlu receptors are primarily presynaptic, however, mGlu1 and mGlu5 receptors (group I) are predominantly found postsynaptically [14]. The mGluR3 and mGluR5 receptors are expressed by astrocytes as part of the tripartite synapse [15]. Glutamate is the neurotransmitter at the vast majority of excitatory synapses in the brain, and mGlu receptors act as important pre- and postsynaptic regulators of neurotransmission in the central nervous system, providing a mechanism by which fast synaptic responses through ligand-gated cation channels can be adjusted [16]. Thus, mGlu receptors are controlled to participate in a wide variety of functions of the central nervous system. So far, major drug discovery programs have largely focused on group I (mGlu1 and mGlu5) and II (mGlu2 and 3) mGlu receptors, which have been implicated in neuropathological and various psychiatric disorders [17]. The activation of group II mGlu receptors (mGlu2 and mGlu3), which couple through Gi/Go leading to inhibition of neuronal transmission, has proven effective in some experimental models of PD [18]. The group III mGlu receptors (mGlu4, mGlu6, mGlu7 and mGlu8) have been gradually understood. All but mGlu6, which is expressed only in the retina, receptors play important neuromodulatory roles in the brain [19]. The mGlu4 receptor contributes substantially to the high-affinity binding site for amino-4-phosphonobutyrate in several regions of brain including substantianigra and hippocampal dentate gyrus [20]. Three receptors from group III (mGlu4,
mGlu 7, and mGlu 8) are of interest because their presynaptic activation reduces neurotransmitter release, which are found on pre-synaptic terminals of basal ganglia pathways whose overactivity is implicated not only in the generation of motor symptoms in PD, but also in driving the progressive substantia nigra degeneration. [21,22,]. The concept of group III mGlu receptors activation to improve parkinsonian symptoms has been suggested [23]. Recent advances also revealed important insights into the potential role of the group III receptors in the pathophysiology of mood disorders [17]. So, activation of the mGlu4 receptor seems to be beneficial for treating both Parkinson-like symptoms and mood disorders [17]. Similarly, genetic inactivation studies support the involvement of the mGlu8 receptor for anxiety disorders [17,24]. Accordingly, modulating mGlu and mGlu receptors has emerged as an attractive promising treatment for PD, depression, and neuroinflammation [25]. Group II mGlu receptors, mGlu2 and mGlu3 receptors, regulate AKT and Wnt signaling and LY379268, a potent mGlu2/3 receptor agonist, treatment has overlapping effects with D2 dopamine receptor antagonists [26]. In addition, granule cells respond to the group III mGlu receptors agonist with an increased phosphorylation of PI3K and AKT [27]. Furthermore, basal synaptic transmission relies on persistent activity of the mGlu receptors, PI3K and mammalian target of rapamycin (mTOR) [28]. Increased glutamate transmission contributes to the symptoms in PD [29].

3. FUNCTION AND CHARACTERIZATION FOR THE PI3K/AKT/PTEN PATHWAY

PI3K is a class of lipid kinase that phosphates PIP2 to generate PIP3, which in turn activates AKT and other effectors. The PI3K pathways are well-known as regulating metabolism, cell growth, and cell survival [30]. Active form of PI3K is an oncogene, and amplifications and mutations of the PI3K are commonly found in many kinds of human cancers [30,31]. The PI3K in mammalian cells forms a family that can be divided into three classes based on the structure, distribution, and mechanism of activation [32]. Class I PI3Ks are further divided into class IA and class IB based on different associated adaptors. Class IA PI3Ks are activated by receptor tyrosine kinases, while class IB PI3Ks are activated by the G-protein-coupled receptors such as the mGlu receptors. These PI3Ks are heterodimers consisting of a regulatory subunit such as p85 and a catalytic subunit such as p110. The phospholipid second messengers generated by the PI3Ks provide a common mechanism for multiple steps during the cellular signal transduction. The AKT (also known as PKB, protein kinase B) is a major downstream target of the PI3Ks. Human AKT has three isoforms: AKT1, AKT2, and AKT3 [33]. The PI3P, a product of PI3K, binds to AKT and leads to the membrane recruitment of the AKT, and also binds to phosphoinositide-dependent kinase 1 (PDK1) via their plekstrin homology (PH) domains, then PDK1 phosphorylates AKT in the kinase domain (Thr 308 in AKT1). For the full activation of AKT, the phosphorylation within the carboxyl-terminal regulatory domain (Ser 473 in AKT1) of AKT by PDK2 is required [34]. Schematic structure of the predicted AKT1 protein is shown in Fig. 2. Once activated, AKT moves to the cytoplasm and nucleus, where it phosphorlates, activates, or inhibits many downstream targets to regulate various cellular functions (Fig. 3). AKT inhibits the GTPase-activating protein (GAP) activity of the tuberous sclerosis complex 1 (TSC1) and TSC2 complex by phosphorylating TSC2 tuberin protein, leading to the accumulation and activation of the mTOR complex [35]. The mTOR mediates the phosphorylation of the ribosomal protein S6 kinases and eukaryotic translation initiation factor 4E-binding protein 1 leading to the release of the translation initiation factor eIF4E [36] (Fig. 3). Suppression of the PI3K/AKT/mTOR signaling modulates PARKIN expression [37], which is an ubiquitin ligase involved in PD. Glycogen synthase kinase 3 (GSK-3) is also a serine/threonine kinase
that was initially identified as playing a role in the regulation of glycogen synthesis in response to insulin receptor stimulation [38]. This molecule has also been shown to be involved in cellular proliferation, programmed cell death, embryogenesis and circadian entrainment, in addition to the regulation of glycogenesis [39]. Neuroprotective mechanisms in response to estrogen have been shown to transmit via the GSK3 signaling [40]. In addition, the PI3K/AKT signaling pathway may mediate the potential neuroprotective effect in mouse model of PD [41].

Phosphatase and tensin homolog (PTEN) is a dual-specificity phosphatase which has protein phosphatase activity and lipid phosphatase activity that antagonizes PI3K activity [42]. Schematic structure of the predicted PTEN protein is shown in Fig. 2. PTEN negatively regulates the PI3K and hence the AKT signaling through converting phosphatidylinositol 3,4,5-triphosphate (PIP3) into phosphatidylinositol 4,5- bisphosphate (PIP2) [43]. PTEN activity can be regulated by the post-translational regulation including phosphorylation, acetylation, and oxidation [44]. PTEN protein consists of N-terminal phosphatase, and C-terminal C2, and PDZ (PSD-95, DLG1, and ZO-1) binding domains. The PTEN CX5R(S/T) motif resides within an active site that surrounds the catalytic signature with three basic residues, which are critical for PTEN lipid phosphatase activity. The structure endows PTEN with its preference for acidic phospholipid substrates such as PIP3. In addition, the C-terminus of PTEN contains two PEST (proline, glutamic acid, serine and threonine) sequences involved in protein degradation [45]. AKT activation leads to HIF-1α stabilization, whereas PTEN attenuates hypoxia-mediated HIF-1α stabilization [46]. The instability of mutant PTEN and the reduction of HIF-1α degradation have been shown to involve protein interactions. Tissue-specific deletion of PTEN can result in autoimmunity, glucose dysregulation or neurological deficits, in addition to carcinogenesis. In addition, PTEN may be involved in a disease state such as Parkinson’s disease (PD) [47]. Several lines of evidence imply that genes associated with familial PD regulate cell death and/or the cell cycle related to AKT/PTEN pathway. For example, deletions of Parkin, a PD related gene, in Drosophila result in AKT activation [48]. Furthermore, PTEN-induced putative kinase 1 (PINK1), which encodes a kinase downregulated in the absence of PTEN, has been identified as the sixth locus (PARK6) associated with familial PD [49]. PINK1 is transcriptionally transactivated by the PTEN gene. The biochemistry of the neurodegeneration in PD points to mitochondrial oxidative stress as the mechanism driving neuronal cell death [8]. The PINK1 is a mitochondrially targeted serine/threonine kinase, which is linked to autosomal recessive early onset PD [50]. The PINK1 may exert a protective effect on the cell that is abrogated by the mutations, resulting in increased susceptibility to cellular stress. These findings provide a molecular link between mitochondria and the pathogenesis of PD.
Fig. 2. Schematic structures of AKT1, mTOR, and PTEN proteins. The predicted consensual domain structures for each protein are depicted. The functionally important sites including the sites of protein phosphorylation are also shown. Note that the sizes of protein are modified for clarity. PH domain = pleckstrin homology domain; C2 domain = a protein structural domain involved in targeting proteins to cell membranes; PDZ = a common structural domain in signaling proteins (PSD95, Dlg, ZO-1, etc); HEAT = huntington, elongation factor 3, a subunit of PP2A and TOR1; FAT = FRAP-ATM-TRRAP; FRB = FKBP12-Rapamycin Binding; FATC = FAT-C-terminal.

Fig. 3. Schematic representation of PI3K/AKT/GSK3/mTOR signaling in cells. Examples of molecules known to act on the regulatory pathways are shown. Note that some critical pathways have been omitted for clarity.
4. PI3K/AKT SIGNALING IS INVOLVED IN THE ACTIONS OF ANTIPSYCHOTICS

While atypical antipsychotic agents are often used for the treatment of PD with psychosis, adverse effects including extrapyramidal symptoms often hinder its continuation. Antidepressants may be effective for PD with psychosis, especially for the visual hallucinations, without worsening the motor symptoms [51]. Antidepressants acting on serotonin neurotransmission have been reported to activate AKT and inhibit GSK3 [52,53]. Several psychoactive drugs have also been shown to modulate the activity of the AKT/GSK3 signaling. AKT has a diverse array of known substrates including the GABA (B) receptor [54]. Indeed, reductions in AKT activation in neurons may increase excitability through reductions in GABA neurotransmission [55]. Drugs like SSRIs and MAO inhibitors that elevate serotonin synaptic transmission have been shown to inhibit GSK3 [56]. On the contrary, drugs that elevate dopamine neurotransmission reduce the inhibitory phosphorylation of GSK3 and therefore increase the kinase activity [57]. By blocking dopamine D2 receptors, classic antipsychotics can prevent the inhibition of AKT by dopamine and concomitant activation of GSK3 [58]. Atypical antipsychotics are also antagonists of serotonin receptors and may interfere with the regulation of GSK3 by the serotonin [59]. Such regulation of AKT and GSK3 activity has also been reported in mice after treatment with haloperidol [60]. Interestingly, AKT/GSK3 pathway is thus regulated by different types of psychiatric drugs. Lithium activates PI3K itself, which in turn results in PI3K-dependent phosphorylation and activation of the AKT, then phosphorylation and inactivation of the GSK3 [61], protecting against neuronal toxicity. Glutamate-induced reduction of AKT activity as well as the associated neuronal toxicity and caspase-3 activation in apoptosis pathways are prevented by the lithium treatment [62]. The mood stabilizers such as valproate have also been reported to inhibit GSK3 [63]. In addition, direct inhibition of GSK3 isoforms has been shown to have effects that are similar to some of those of antidepressants in animal models [64]. Activation of AKT and inhibition of GSK3 may be characterized as fundamental effects for some shared action of psychoactive drugs.

Guanosine has a neuroprotective effect in a cellular oxidative stress model, which increases AKT and GSK3β phosphorylation confirming this pathway plays an important role in the neuro-protective effect [65], suggesting that it could represent a new potential pharmacological tool to be studied in the therapeutic approach to PD [66]. Actually, Protective activity of guanosine in an in vitro model of PD has recently been reported [66]. Guanosine produces an antidepressant-like effect through the modulation of the PI3K/AKT/mTOR pathway [67]. The guanosine also induces the antioxidant enzyme HO-1 expression. The protective effects of guanosine are partially prevented by HO-1 inhibitor, SnPP. In addition, bilirubin, an antioxidant and physiologic product of HO-1, is protective against oxidative stress. When blocking the AKT pathway with LY294002, a selective inhibitor of PI3K, the neuro-protective effect of guanosine is abolished. Zinc protoporphyrin IX (ZnPP), a selective inhibitor of HO-1, attenuates apoptosis and oxidative stress in PC12 neuronal cells [68]. As H2O2 preconditioning enhances phosphorylation of AKT, treatment with the LY294002 before H2O2 preconditioning blocks not only H2O2-induced HO-1 induction, but also the protective effect of H2O2 preconditioning against the cytotoxicity. In this way, increasing evidences pointing to AKT pathway-modification in depression provide a novel implication of antidepressant mechanisms.
5. DISCUSSION AND PERSPECTIVE

Although the evidence for the link between group III mGlu receptors and the PI3K/AKT pathway in the situation of PD is not clearly established, activation of the mGlu receptors/PI3K/AKT signaling pathway may play a critical role in the mechanisms of PD. Otherwise, modulation of neurotransmission via presynaptic mechanisms by group III mGlu receptors might provide protection against neuro-degeneration in PD. However, prodigious evidence supports the group III mGlu receptors as potentially important drug targets for providing both symptom help and neuroprotection in PD [21, 22]. Indeed, the group III mGlu receptors may be promising targets for drug discovery in PD. It is speculated that improvement or modulation of these signaling pathways will reveal potential therapeutic targets. In particular, the mGlu4 receptor subtypes may be an efficient target for PD treatment, and open promising perspectives for the development in the pharmacological resource for this disease. Positive modulation of the ligand of the mGlu receptor remains one of the attractive non-dopaminergic therapies for PD as well as for accompanied indications such as pain, depression, and diabetes [25]. Similarly, selective ligands of mGlu7 receptor subtypes may also be considered as promising compounds for the development of antiparkinsonian therapeutic strategies. However, the possible precise involvement of the PI3K/AKT/PTEN/GSK3/mTOR in neuropsychiatric cell signaling has remained unexplored. Between neuro-degeneration and neurogenesis, there might be common pathways including the PI3K/AKT pathway. Whereas many questions remain to be answered about the role of the PI3K/AKT signaling in PD and mental disorders, it is possible that inhibition of the signaling in specific neuronal populations could be associated with distinct behavioral outcomes. The challenge of treatment could be a trade-off between the emergence of the side-effects and the amelioration of the disease. More understanding of the intracellular mechanisms downstream of PI3K/AKT/PTEN changes in PD could provide novel insights into the development of new therapeutic approaches having superior efficacy against the disease.

6. CONCLUSION

The mGlu receptors may be coupled to the phosphatidylinositol-3-kinase (PI3K), AKT, and PTEN pathways, which play a central role in cell survival and play a critical role in the mechanisms of PD. Modulation of neurotransmission via presynaptic mechanisms by group III mGlu receptors might provide protection against neuro-degeneration.

CONSENT

Consent section is not required.

ETHICAL APPROVAL

Ethical approval section is not required.

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COMPETING INTERESTS

The authors declare that they have no competing financial interests.

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