Emerging Nondopaminergic Medications for Parkinson's Disease: Focusing on A2A Receptor Antagonists and GLP1 Receptor Agonists

Pei Shang, Matthew Baker, Samantha Banks, Sa-Ik Hong, Doo-Sup Choi

Departments of Molecular Pharmacology and Experimental Therapeutics, Neurology, Psychiatry and Psychology, Neuroscience Program, Mayo Clinic, College of Medicine, Rochester, MN, USA

ABSTRACT

Parkinson’s disease (PD) is a severe neurodegenerative disease characterized by classic motor features associated with the loss of dopaminergic neurons and appearance of Lewy bodies in the substantia nigra. Due to the complexity of PD, a definitive diagnosis in the early stages and effective management of symptoms in later stages are difficult to achieve in clinical practice. Previous research has shown that colocalization of A2A receptors (A2AR) and dopamine D2 receptors (D2R) may induce an antagonistic interaction between adenosine and dopamine. Clinical trials have found that the A2AR antagonist istradefylline decreases dyskinesia in PD and could be used as an adjuvant to levodopa treatment. Meanwhile, the incretin hormone glucagon-like peptide 1 (GLP1) mainly facilitates glucose homeostasis and insulin signaling. Preclinical experiments and clinical trials of GLP1 receptor (GLP1R) agonists show that they may be effective in alleviating neuroinflammation and sustaining cellular functions in the central nervous system of patients with PD. In this review, we summarize up-to-date findings on the usefulness of A2AR antagonists and GLP1R agonists in PD management. We explain the molecular mechanisms of these medications and their interactions with other neurotransmitter receptors. Furthermore, we discuss the efficacy and limitations of A2AR antagonists and GLP1R agonists in clinical practice.

Keywords A2A receptor antagonist; GLP1 receptor agonist; Parkinson’s disease.

INTRODUCTION

Parkinson’s disease (PD) is a progressive and degenerative disorder characterized pathologically by a substantial loss of dopaminergic neurons in the substantia nigra. PD is a relatively well-characterized disorder, and objective clinical assessment provides accurate diagnosis and analysis of disease severity. To reverse the dopamine deficiency that drives symptoms in PD, levodopa (L-DOPA), a precursor of dopamine that readily crosses the blood-brain barrier (BBB), revolutionized PD treatment since its Food and Drug Administration (FDA) approval in 1962. Many additional therapeutic drugs used as combinatory treatments work through different mechanisms, such as inhibiting L-DOPA or dopamine metabolism or activating dopamine receptors. Although the efficacy of dopamine-based treatment for PD symptoms is broadly well accepted and tolerable, the fluctuation in dopamine levels in the brain may result in potential side effects, including levodopa-induced dyskinesia (LID), impulsivity, and sleep disturbance. Numerous novel drugs have been tested in clinical trials to mitigate dopamine-based treatment shortcomings or reverse or compensate for dopamine deficiency. In 2019, the FDA approved a novel nondopaminergic medication, istrade- 
fylline, an adenosine A<sub>2A</sub> receptor (A<sub>2A</sub>R) antagonist, as an adjuvant drug to treat off-episodes of PD symptoms. Interestingly, the glucagon-like peptide-1 receptor (GLP1R) agonist exenatide is another emerging nondopaminergic receptor-based treatment option and shows promising preclinical and clinical outcomes. In this review, we discuss how these two G-protein coupled receptor (GPCR) ligands may improve L-DOPA-based treatment with minimized side effects or provide alternative nondopaminergic options for patients who would benefit from early treatment.

**ADENOSINE A<sub>2A</sub>R ANTAGONISTS**

**Adenosine and adenosine receptors in movement**

Adenosine and its receptors have been considered important therapeutic targets for PD due to their neuromodulatory and homeostatic functions in the human brain. Generally, adenosine receptors have been divided into subtypes, including A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>. As an endogenous purine nucleoside, adenosine modulates several physiological functions in the central and peripheral nervous systems. Under basal conditions, adenosine mainly acts on inhibitory A<sub>1</sub> receptors (A<sub>1</sub>R) and excitatory A<sub>2A</sub>Rs to integrate dopamine and glutamate signaling, which controls the synaptic plasticity associated with learning, memory, and cognition. Adenosine preferentially acts at A<sub>1</sub>R because of its widespread distribution and high expression levels. The A<sub>2A</sub>R is a GPCR that can activate adenylyl cyclase. Of note, A<sub>2A</sub>R is always distributed and colocalized with dopamine D<sub>2</sub>R and D<sub>3</sub>R on striatopallidal neurons in the striatum. A<sub>2A</sub>R can also interact with dopamine D<sub>2</sub>R and reduce the expression of D<sub>2</sub>R (Figure 1). Due to their localization in the basal ganglia, A<sub>2A</sub>R modulates the indirect pathway by modulating gamma-aminobutyric acid (GABA) and glutamate release, both of which are highly involved in the control of voluntary movements.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Possible mechanisms of A<sub>2A</sub>R antagonists on PD. A<sub>2A</sub> receptors and dopamine D<sub>2</sub> receptors interact with each other, and A<sub>2A</sub> receptor activation inhibits the function of the D<sub>2</sub> receptor under normal conditions. A<sub>2A</sub> receptor antagonists can be adjuvants to D<sub>2</sub>R agonists, diminishing the inhibition of the D<sub>2</sub> receptor by adenosine. Thus, A<sub>2A</sub>R antagonists block the effects of adenosine and facilitate D<sub>2</sub>R agonist effects on lowering cAMP levels and then dampens PKA activity, which may result in neuroprotective effects. Meanwhile, the combination of an A<sub>2A</sub> receptor antagonist and mGluR5 antagonist also promotes neuroprotection and activates the indirect corticostriatal circuit while reducing PD-like symptoms. The synergistic effect of A<sub>2A</sub>R antagonist, D<sub>2</sub>R agonist, and 5-HT<sub>1A</sub>/1BR agonist also prevents L-DOPA-related dyskinesia-like behaviors. Figure 1 was modified from Nazario et al. 5-HT: serotonin, A<sub>2A</sub>R: adenosine A<sub>2A</sub> receptor, cAMP: cyclic adenosine monophosphate, D<sub>2</sub>R: dopamine receptor D<sub>2</sub>, L-DOPA: levodopa, LTP: long-term potentiation, mGluR5: metabotropic glutamate receptor 5 receptor, PD: Parkinson’s disease, PKA: protein kinase A.
emerge after long-term utilization of dopaminergic agonists. Although surgical interventions such as deep brain stimulation (DBS) can effectively relieve bradykinesia, rigidity, and tremor in PD patients, DBS has several limitations, including the risk of surgical complications and affordability. Istradefylline, an A2AR antagonist, was approved by the FDA as an anti-PD drug in 2019. Importantly, istradefylline exhibited powerful increases in locomotor activity and potentiated dopaminergic agonist motor effects in animal models of PD (Table 1). Indeed, dysfunction in adenosinergic transduction is associated with neurological disorders ranging from epilepsy to neurodegenerative disorders. Not surprisingly, the adenosinergic system was identified to be dysregulated in patients with PD. Researchers also demonstrated increased A2AR density in the caudate-putamen from PD subjects in a postmortem study. Consistently, pharmacological inhibition by A2AR antagonists has been found to improve motor behavior deficits in PD and dyskinesia. Interestingly, a photoactive adenosine A2AR antagonist also showed potential to remotely control movement disorders such as PD.

A2AR antagonism was first identified for potential therapeutic effects in patients with PD with the antimalarial drug mefloquine, which contains an A2AR antagonist. Experimentally, periodically interrupted or long-lasting administration of an A2AR antagonist such as SCH58261 combined with L-DOPA may restore normal motor function in PD animal models. Interestingly, long-acting L-DOPA treatment also results in an enhanced biosynthesis of A2ARs in patients with PD-induced dyskinesias, especially in brain networks involving the striatum and substantia nigra.

### Interactions between adenosine A2AR and other GPCRs in PD

The hypothesis for A2AR antagonist utilization in PD is based on adenosine-dopamine antagonism in the striatum, which has the highest expression of A2AR in the human body. Accumulated evidence has verified the functional relationships between A2AR and D2R in the basal ganglia (Figure 1). Researchers have also identified D/R/A2AR oligomers in the mouse and monkey striatum via proximity ligation assays, immunoelectron microscopy, and ligand fluorescence resonance energy transfer (FRET)-based approaches. In addition, D/R/A2AR oligomers in the striatum have been postulated to appear at the onset of PD and could interrupt selective dopaminergic denervation. Furthermore, A2AR mRNA has been detected in striatal cholinergic interneurons according to a previous study. Due to structural associations, A2AR activation can inhibit Gα protein (G protein α subunit), which inhibits adenyl cyclase activity and thereby decreases

### Table 1. Summary of clinical trials of A2AR antagonists for PD with symptom improvements

| Medication | Trial design | Subjects | Treatment doses | Outcomes | Reference |
|------------|--------------|----------|----------------|----------|-----------|
| Istradefylline | A phase 2, double-blind, placebo-controlled study of istradefylline in PD patients on L-DOPA/carbidopa | 790 PD patients with an average OFF time at least 2 h/day and approximately 3.2 years after diagnosis | 20 (for 163 subjects) or 60 mg (for 155 subjects) per day | Significant reduction in the awake time per day spent in OFF state | 119 |
| Istradefylline | A phase 3, multicenter, open-label, long-term (52 w) study of istradefylline in PD patients experiencing wearing-off | 313 PD patients approximately 7.5 years after onset and 3.3 years after showing motor complications | 20 mg as starting dosage with/o adjustment to 40 mg | Significant OFF time reduction since the 2nd week | 120 |
| Istradefylline | Istradefylline as adjunctive treatment to levodopa for 12 weeks in a phase 3, double-blind manner in PD patients with motor complications | 373 PD patients 3.3 years after showing motor complications | 20 or 40 mg per day | Istradefylline markedly reduced daily OFF time and was well-tolerated in patients with motor complications | 121 |
| Istradefylline | A phase 3 randomized, 12-week, double-blind, placebo-controlled parallel-group study of istradefylline with different doses in patients on levodopa therapy | 610 PD patients with an average OFF time at least 3 h/day, 9 years after diagnosis, and 3.6 years after motor fluctuations | 10, 20, and 40 mg per day | Istradefylline did not impact daily OFF time but significantly improved motor scores at 40 mg per day | 122 |
| Tozadenant | A phase 2, double-blind, randomized, placebo-controlled study of tozadenant as adjunctive therapy in L-DOPA-treated PD subjects | 337 PD patients with an average OFF time at least 6 h/day and 8.7 years after diagnosis | 60 or 120 or 180 or 240 mg/BID | Tozadenant significantly reduced daily OFF time and improved motor signs without increasing dyskinesia | 123 |
| Preladenant | A phase 2, 36-week, open-label, follow-up safety study of SCH420814 in subjects with PD | 140 PD patients with moderate to severe PD > 5 years | 5 mg/BID | Long-term preladenant treatment are well-tolerated and sustained the OFF time reduction | 124 |

A2AR: adenosine A2A receptor, BID: twice a day, L-DOPA: levodopa, PD: Parkinson’s disease.
cAMP levels) coupled with D2R, further validating the existence of the A2AR-D2R heteroreceptor complex.34,35

Meanwhile, D3R activation can lead to the formation of D3R-NMDAR heteroreceptor complexes and subsequent inhibition of NMDAR signaling.36 Overactivity of astroglial A3AR induces extrasynaptic and postsynaptic mGluR1 and mGluR5 coupling to Gq protein (G protein α subunit, which activates phospholipase β and thereby increases diacylglycerol and inositol-triphosphate levels) by enhancing astroglial glutamate release, which can further increase intracellular calcium levels and lead to inhibition of D1R signaling in A3AR-D2R and A3AR-mGluR5 complexes (Figure 1).37 The A3AR-D2R and A3AR-mGluR5 complexes may inhibit D2R promoter recognition and activate intracellular MAPK and CREB signaling pathways, mainly relying on antagonistic allosteric receptor-to-receptor interactions.38,39 Nonetheless, A2AR activation by adenosine may have an excitatory effect on striatopallidal neurons in a D2R-independent manner.40-41

During the early phase of PD, L-DOPA and D3R agonists can prevent D2R promoter inhibition induced by the basal A3AR promoter since more D2R homoreceptor complexes are expressed than A2AR-D2R complexes.42 5-HT1A/1B agonists combined with A2AR antagonists were also reported as an advanced therapy for PD with antidyskinetic effects, implicating a potential synergic effect between the two receptors (Figure 1).43

Adenosine A2AR antagonists on cognition

Cognitive impairment frequently occurs in patients with PD and usually reduces patient quality of life and comfort.44 Early cognitive deficits in PD were hypothesized to be associated with deficits in dopaminergic innervation of the cortex and alterations in striatum-thalamocortical loop function, which is difficult to manage using dopaminergic medications.45,46 Interestingly, A2AR antagonists improve cognitive functions, including memory. The A2AR antagonist SCH58261 improved memory performance and social recognition memory in rodent models with memory deficits.47 However, A2AR antagonist administration into the posterior cingulate cortex impaired the process of memory retrieval in rats,48 suggesting region-specific effects. In practice, donepezil, an acetylcholinesterase inhibitor, is commonly prescribed for patients with PD to manage cognitive impairment and memory loss and might be an adjuvant to A2AR antagonists to alleviate side effects.49

A2AR antagonists, including ZM241385 and istradefylline, may restore social recognition and cognitive deficits in rats.50,51 Similarly, A2AR antagonists or genetic deletion of A2AR were shown to improve short-term memory, working memory, reversal learning, goal-directed behavior, and fear conditioning in animal models used for different neurological diseases.52-56

Adenosine A2AR antagonists: efficacy and limitations

It has been clinically verified that A2AR antagonists can improve motor dysfunction in patients with PD as monotherapy or in combination with L-DOPA and other antiparkinsonian drugs (Table 1).57-63 Previous clinical trials have also shown that A2AR antagonists are effective in shortening the off-time without worsening troublesome dyskinesias and increasing on-time in patients with advanced stage PD and L-DOPA treatment.59 However, with the exception of istradefylline, almost all of the other clinical trials with novel therapeutics have failed in recent years, including preladenant, vipadenant, and the nonxanthine SCH58261.59,60 Clinical trials of the A2AR antagonist named preladenant were discontinued due to the lack of efficacy.61 Side effects induced by A2AR antagonists, including insomnia, headache, constipation, hallucinations, and cardiac failure, merit attention from caregivers.62 Targeting A2AR with classic pharmacology has shown some drawbacks, including slow and imprecise drug delivery and low specificity and efficacy.21 A2AR antagonists generally have higher molecular weights and are difficult to synthesize due to the complexity of structures, poor water solubility, and furan groups that preclude replacement by classic chemistry.63 Caffeine is an adenosine analog and has been shown to confer neuroprotection against dopaminergic neurodegeneration via modulation of A2AR pathways and neuroinflammation in PD models.64 Furthermore, caffeine was demonstrated to improve motor function in PD patients by targeting A2AR.65 Chronic caffeine treatment can largely attenuate α-synuclein-induced microglial activation and astrogliosis in mice, similar to A2AR antagonists.66,67 However, a clinical trial has shown that caffeine intake twice daily (200 mg) over 6 months did not produce significant symptomatic benefits for patients with PD.68 Therefore, further studies are required to clarify the benefits of caffeine for the prevention or improvement of early or moderate PD symptoms.

Interestingly, our preclinical experiment showed that A2AR inhibition increases alcohol-seeking behaviors69 through enhanced goal-directed cognitive function. Consistent with this finding, pharmacological activation of A2AR or optogenetic activation of A2AR-expressing neurons in the dorsomedial striatum (DMS) decreases alcohol-seeking behaviors.70 In corticostriatal circuits, A2AR-expressing neurons consist of indirect and inhibiting circuits, as discussed in the previous section. Adenosine is known to mediate the intoxicating effect of alcohol,71-73 and A2AR inhibition may increase reward-seeking behaviors when subjects are introduced to addictive substances or activities. As noted above, A2AR inhibition increases cognitive function through enhanced goal-directed behavior. Even though istradefylline was suspected to positively affect cognitive dysfunction and postural abnormalities in patients with PD, short-term clinical trials did not show benefits on cognition.74 Meanwhile, based on preclinical studies,
A2AR inhibition may increase the risk of addiction. Therefore, it is important to monitor the behavioral patterns of PD patients when A2AR antagonists are prescribed.

**GLP1R AGONISTS**

Glucagon-like peptide and GLP1R-mediated signaling in insulin regulation

Glucagon-like peptide-1 (7-36) amide (GLP1) is secreted from intestinal enteroendocrine L cells in response to food intake and controls systemic blood glucose homeostasis in the human body. The intestinal wall secretes GLP1 to activate enteroenic reflexes, control gastric motility, and slow gastric emptying. GLP1 also activates vagal sensory nerve terminals and initiates vagal-vagal autonomic reflexes by controlling the endocrine function of the pancreas. The islets of Langerhans in the pancreas can be stimulated by GLP1 and release insulin to inhibit glucagon production. GLP1Rs are usually expressed in hypothalamic neurons and vagal afferent ganglion neurons. Due to rapid degradation and short half-lives, only 10–15% of GLP1 reaches circulation after release. Peripheral injection of GLP1R antagonists facilitates food intake and diminishes the efficacy of circulating GLP1, suggesting that the feeding process induced by GLP1 relies on peripheral GLP1R, which activates vagal afferents after stimulation. Notably, the glucose-lowering function of GLP1 is highly dependent on the concentration of glucose. This property of GLP1 prevents it from lowering blood glucose after fasting. Therefore, GLP1R agonists are clinically used as a new class of glucose-controlling agents for treating type 2 diabetes (T2D) without introducing the side effects of hypoglycemia.

Based on previous findings, GLP1 may not influence the metabolome or directly interact with rodent β cells, and short-term exposure to GLP1 did not induce changes to glycolytic or TCA cycle intermediates [*in vitro*]. The binding between GLP1 and GLP1R on various cells can activate adenylate cyclase and increase cAMP levels, which further stimulates protein kinase A and cAMP-regulated guanine nucleotide exchange factor 2 pathways and insulin secretion. A previous study also found that GLP1 may stimulate the secretion of insulin in β cells and induce glucose metabolism via the mTOR-dependent HIF-1α activation pathway.
As a promising therapeutic strategy for the management of T2D, GLP1 efficacy has been compared with different insulin formulations, including glargine and detemir, in multiple clinical trials. Long-acting GLP1R agonists have shown better glycemic efficacy than basal insulin. For instance, a once-weekly regimen of semaglutide significantly decreased the HbA1c levels compared with glargine therapy.

GLP1R and dopaminergic neurons

While GLP1R plays an important peripheral role in glucose-dependent insulin secretion and gene expression, there is increasing evidence of its central role in feeding and satiety-related behaviors. GLP1R expression has been observed throughout the brain in both rodents and humans. In particular, GLP1R is highly expressed in mesolimbic reward pathways, including the hypothalamus, ventral tegmental area, lateral septum, nucleus of the solitary tract, and many others. GLP1 and other GLP1R agonists have been shown to cross the BBB. GLP1R is a G-protein-coupled GPCR that activates adenylyl cyclase, leading to increased intracellular cAMP levels (Figure 2). GLP1R activation has been shown to directly interact with the dopamine system by decreasing phasic dopamine release and facilitating a reduction in feeding and reward-seeking behaviors. Additionally, GLP1R stimulation has been shown to exert neuroprotective and neuroproliferative effects in response to stroke, neurodegeneration, and other neurologic injuries (Figure 2).

In particular, exenatide, a novel GLP1R agonist that was discovered in the saliva of the Gila monster (Heloderma suspectum), was shown to reduce dopaminergic cell loss in the substantia nigra in a methyl-phenyl tetrahydropyridine (MPTP)-induced mouse model of PD and restore normal dopamine levels and motor function. Similarly, exenatide treatment was shown to reduce dopaminergic cell loss and motor function in rats injected with 6-hydroxydopamine (6-OHDA), another toxin that selectively causes dopaminergic cell death. In addition to motor effects, GLP1R has been shown to have a neuroprotective role in cognitive function through enhanced synaptic plasticity. While GLP1R null mouse models have shown evidence of impaired long-term potentiation (LTP) and learning and memory deficits, GLP1R stimulation increases LTP and restores cognitive function in neurodegenerative mouse models.

The extended-release form of the protease-resistant and brain-penetrating exenatide was approved by the FDA for T2D in 2018. Following this, Dr. Foltynie’s group in England demonstrated that weekly administration of exenatide for 48 weeks significantly improved PD symptoms in a phase II clinical trial. Recently, improved extended-release forms of exenatide with increased brain penetration and longer bioavailability were developed. Since various forms of exenatide were comprehensively tested in humans through T2D clinical studies, the new application of exenatide in PD will be available for PD treatment in the near future.

GLP1R agonists: efficacy and limitations

GLP1 function is hypothesized to be a pivotal molecular pathway in glucose regulation via the gut-brain axis. Interestingly, GLP1R is expressed not only in peripheral organs such as the pancreas but also in the brain. In line with this theory, GLP1R agonists showed positive impacts on controlling cardiovascular diseases, especially in patients with diabetes. Liraglutide, a GLP1R agonist, has been implicated as an efficient weight-loss agent in patients with or without T2D. GLP1R agonists such as exenatide have also been demonstrated to exert neuroprotective and neurotrophic effects and have shown therapeutic efficacy in PD management in several clinical and preclinical trials (Table 2 and 3). Another GLP1R agonist, lixisenatide, can cross the BBB and increase cAMP levels at a low dose. GLP1R activation elicits neurite outgrowth of SH-SY5Y cells, similar to the function of nerve growth factors, further validating its potential role in neurogenesis and neurotrophism. Meanwhile, exenatide induces approximately twofold changes in doublecortin-positive cells in the medial striatum and bromodeoxyuridine-positive cells in the subventricular area in adult mice, both of which are highly involved in the process of neurogenesis. Exenatide also improves Mattis dementia rating scale scores in patients with PD. The follow-up study showed that the benefits lasted for 12 months after the cessation of exenatide. The neuroprotective mechanisms of GLP1R agonists have not been elucidated until now. The brain-penetrant long-acting GLP1R agonist NLY01 prevented the loss of dopaminergic neurons and improved behavioral deficits in an α-synuclein-treated fibril model mimicking sporadic PD. NLY01 prolonged life expectancy and alleviated neurodegeneration and neuropathological abnormalities in the human A53T α-synuclein (hA53T) transgenic mouse model. The neuroprotective effects of the GLP1R agonist are likely correlated with the MAPK (ERK) and PI3K/AKT pathways (Figure 2).

CONCLUSIONS

This review provides current perspectives on the recently approved istradefylline and the recently investigated exenatide as new treatment options for PD. Ongoing postmarketing clinical studies on istradefylline will reveal optimal dosing and treatment timing for PD symptom management. Regarding exenatide, as it is clinically used for T2D, additional trials will inform the potential benefits in PD and T2D. Furthermore, various suspended release forms of exenatide will be available for once weekly or every
other week treatment regimens. More user-friendly routes of administration (pencil-type syringe or oral form) will increase the accessibility of this novel medication. Importantly, we need to develop personalized treatment methods for PD based on more precise phenotyping and genotyping, which may correlate with the treatment outcomes associated with existing and novel medications. Big-data-driven artificial intelligence will eventually aid physicians' treatment strategies with improved symptom monitoring systems.

Conflicts of Interest

D.S.C. is a scientific advisory board member for Peptron Inc. Peptron had no role in the preparation, review, or approval of the manuscript or the decision to submit the manuscript for publication. All the other authors declare no biomedical financial interests or potential conflicts of interest.

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Table 2. Summary of preclinical trials of GLP1R agonists for PD

| GLP1R agonist | PD models | Treatment details | Experimental results | Reference |
|---------------|-----------|-------------------|----------------------|-----------|
| Ex-4 | 6-OHDA/LPS-treated rat model | Ex-4 (0.1 and 0.5 µg/kg) was given 7 days after the intracerebral toxin injection, BID for 7 days | Circling behavior was attenuated in Ex-4 group; striatal tissue dopamine level increased in Ex-4 group | 125 |
| Ex-4 | 6-OHDA-treated rat model | Ex-4 (0.1 µg/kg) was given 5 weeks after the intracerebral toxin injection, BID for 21 days | Ex-4 protected dopaminergic neurons, preserved dopamine levels and improved motor functions | 97 |
| Ex-4 | MPTP-treated mouse model | Ex-4 (20 nM, 0.25 µL/h) was given 7 days 2 hour before MPTP treatment via left ventricle administration | PT302 increased tyrosine hydroxylase levels in the lesioned substantia nigra and striatum; PT302 reduced the neurodegeneration of nigrostriatal dopaminergic neurons | 126 |
| Extended-release Ex-4 (PT302) | 6-OHDA-treated rat model | Ex-4 (0.4 or 2 mg/kg) was given every 2 weeks for 10 weeks starting 16 days before the unilateral lesion induced by 6-OHDA | | |
| Lixisenatide | MPTP-treated mouse model | Lixisenatide (10 nmol/kg) was given after the 7-day MPTP treatment, once a day for 14 days | Lixisenatide prevented MPTP-induced motor impairment, reduction in tyrosine hydroxylase levels in substantia nigra, and reduction in pro-apoptotic signaling | 127 |

6-OHDA: 6-hydroxydopamine, BID: twice a day, Ex-4: Exendin-4, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, PD: Parkinson’s disease, LPS: lipopolysaccharide, GLP1R: glucagon-like peptide-1 receptor.

Table 3. Summary of phase 2 clinical trials of GLP1R agonists for PD

| GLP1R agonist | Treatment details | Subjects | Study design | Primary outcome measures | Conclusions | Reference |
|---------------|-------------------|----------|--------------|--------------------------|-------------|-----------|
| Ex-4 | Self-administer twice-daily subcutaneous injections of 5 µg for 1 month and 10 µg for 11 months | 45 patients: moderate PD approximately 7.5 years since disease onset | Single-blind, placebo-controlled. 21-Ex-4 and 24-placebo | MDS-UPDRS and nonmotor tests at baseline, 6 months, 12 months, and 14 months | MDS-UPDRS scores in the Ex-4 treated group improved 2.7 points compared with 2.2 in the control group; motor and cognitive functions also improved in Ex-4 treated group | 108 |
| Ex-4 | Once-weekly subcutaneous injections of 2 mg for 48 weeks | 62 patients: moderate PD with DAergic treatment with wearing-off effects | Single-center, randomized, double-blind, placebo-controlled. 32-Ex-4 and 30-placebo. | MDS-UPDRS motor subscale (part 3) | Ex-4 significantly improved MDS-UPDRS scores of patients in the OFF time | 98 |
| Ex-4 | 2 mg of once weekly or placebo for 48 weeks followed by a 12-week washout period | 60 patients: moderate PD; patients were receiving dopaminergic treatment | Single-center, randomized, double-blind, placebo-controlled. 31-Ex-4 and 29-placebo | MDS-UPDRS and serum were collected after 12-week withdrawal; insulin and PKB-related pathways were tested | Ex-4 treated group showed increased phospho-IRS1 and elevated expression of total AKT and phospho-mTOR; improvement of MDS-UPDRS was correlated to total and phospho-mTOR level | 113 |

Ex-4: exenatide-4, mTOR: mechanistic target of rapamycin, IRS1: insulin receptor substrate 1, MDS-UPDRS: Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale, PD: Parkinson’s disease, PKB: protein kinase B, DAergic: dopaminergic, GLP1R: glucagon-like peptide-1 receptor.
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Author Contributions

Conceptualization: Pei Shang, Doo-Sup Choi. Funding acquisition: Doo-Sup Choi. Investigation: all authors. Project administration: Pei Shang, Doo-Sup Choi. Resources: Pei Shang, Matthew Baker, Samantha Banks, Doo-Sup Choi. Supervision: Doo-Sup Choi. Writing—original draft: all authors. Writing—review & editing: all authors.

ORCID IDs

Pei Shang https://orcid.org/0000-0003-4345-2165
Matthew Baker https://orcid.org/0000-0002-5901-598X
Samantha Banks https://orcid.org/0000-0002-5856-1367
Sa-Ik Hong https://orcid.org/0000-0003-4799-739X
Doo-Sup Choi https://orcid.org/0000-0002-6796-9938

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