

Repurposing Retatrutide for Neuroprotection in Parkinson's Disease: A Comprehensive Review

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Publication Date: 2026/10/06

Abstract: Parkinson's disease is a progressive neurodegenerative condition marked by the loss of dopaminergic neurons, mitochondrial dysfunction, oxidative stress, and persistent neuroinflammation. Recent findings suggest that impaired glucose metabolism and disrupted energy balance may play a role in the early stages of the disease's progression. In light of this, therapies based on metabolic hormones have garnered interest for their potential neuroprotective effects. Retatrutide, a new triple agonist that targets GLP-1, GIP, and glucagon receptors, offers a promising therapeutic approach. The activation of these receptors influences crucial intracellular pathways that are involved in neuronal survival, reducing inflammation, and enhancing mitochondrial function. Preclinical research on incretin-based therapies has shown a decrease in dopaminergic neurodegeneration and improvements in motor function. This review delves into the impact of metabolic dysfunction in Parkinson's disease and assesses the therapeutic promise of multi-receptor agonists, with a particular focus on Retatrutide. Although the findings are encouraging, additional clinical studies are necessary to confirm its effectiveness and safety in neurodegenerative diseases.

Keywords: Parkinson's Disease, Retatrutide, Incretin Based Therapy, Neuroprotection, Mitochondrial Dysfunction, Neuroinflammation.

How to Cite: Thilagavathi K.; Sivakumar G.; Narmatha K. K.; Deepika A.; Keerthana S.; Evania Helen M. D. (2026) Repurposing Retatrutide for Neuroprotection in Parkinson's Disease: A Comprehensive Review.

International Journal of Innovative Science and Research Technology, 11(9), 2928-2938.

<https://doi.org/10.38124/ijisrt/26sep1305>

I. INTRODUCTION

1% of adults over 60 Parkinson's disease, recognized as the second most common neurological disorder, affects people globally, and the risk rises with age [1]. The loss of nigrostriatal dopaminergic neurons, which results in the typical motor signs and symptoms of bradykinesia, stiffness, and tremor, is the hallmark of this degenerative condition. Similar disruption of glucose and energy metabolism appears to be an early event in the pathophysiology of sporadic Parkinson's disease, according to mounting data [2]. While insulin is primarily known for its role in regulating glucose levels in the body, it also has protective effects on the brain. Insulin receptors are present in regions like the basal ganglia and substantia nigra. Research increasingly supports the idea that insulin is vital for the survival and growth of neuron, the transmission of dopamine, and the maintenance of synapses [3]. Retatrutide, a new triple agonist that stimulates GLP-1, GIP, and glucagon receptors at the same time, is one intriguing candidate. Retatrutide may help preserve dopaminergic neurons in the Substantia nigra by modulating metabolic and neuroprotective processes, slowing

neurodegeneration. As a result, incretin-based multi-agonists such as Retatrutide provide a viable treatment approach for Parkinson's disease [4].

The purpose of this article was to critically analyse the data regarding the influence of glucose absorption, energy utilisation, and inflammation on the pathogenesis of Parkinson's disease. The possible influence of glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) receptor, and glucagon agonists on these pathways will be discussed next, as will preliminary clinical results for repurposing medications targeting these incretin hormones. Finally, the possibility of new combined GLP-1/GIP/glucagon receptor agonists will be discussed.

➤ Impaired Glucose Metabolism in Parkinson's Disease

Alterations in brain energy metabolism have emerged as a key aspect in Parkinson's disease pathogenesis. Neurones primarily rely on glucose for energy, and poor glucose absorption or utilisation can have a major impact on neuronal survival and function. Neuroimaging investigations utilising 0.18F-fluorodeoxyglucose positron emission

tomography (FDG-PET) have revealed impaired cerebral glucose metabolism in various brain areas of Parkinson's disease patients [5,6]. This decrease in glucose uptake becomes more noticeable as the disease develops, indicating that metabolic dysfunction contributes to neurodegeneration. Impaired insulin signalling inside the brain is one of the major contributors to impaired glucose metabolism in Parkinson's disease. Although insulin does not directly regulate neuronal glucose absorption in the same way as it does in peripheral tissues, it does play an important role in maintaining the expression of glucose transporters and regulating neuronal energy balance. Abnormal insulin signalling pathways have been reported in Parkinson's disease patients, which may lead to poor glucose utilisation and increased neuronal vulnerability.

Epidemiological studies indicate a link between metabolic dysregulation and neurodegenerative diseases. Type 2 diabetics, for example, are more likely to acquire neurological disorders such as Parkinson's disease.

Impaired glucose metabolism and insulin resistance in diabetic patients may accelerate neuronal damage and worsen disease progression. Clinical cohort analyses have shown that Parkinson's disease patients with impaired glucose disposal often exhibit faster disease progression and

increased mortality compared with those with normal glucose metabolism [7-10].

The transport of glucose into the brain is primarily mediated by glucose transporters located at the blood–brain barrier and within neuronal cells. The transporter GLUT1 facilitates glucose transport across the blood–brain barrier, while neurons predominantly express GLUT3, which ensures efficient glucose uptake to meet their high metabolic demands [10]. Evidence suggests that the expression of these glucose transporters may be reduced in neurodegenerative conditions, leading to impaired glucose delivery to neurons and subsequent energy deficits. Such metabolic disturbances may exacerbate mitochondrial dysfunction, oxidative stress, and neuroinflammation—key mechanisms involved in the degeneration of dopaminergic neurons in Parkinson's disease.

Overall, impaired brain glucose metabolism represents a significant contributor to the progression of Parkinson's disease. Understanding the relationship between metabolic dysfunction, insulin signaling, and neuronal survival has stimulated interest in metabolic-based therapeutic strategies. Drugs originally developed for metabolic disorders, such as incretin-based therapies, are currently being investigated for their potential neuroprotective effects in PD.

II. PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

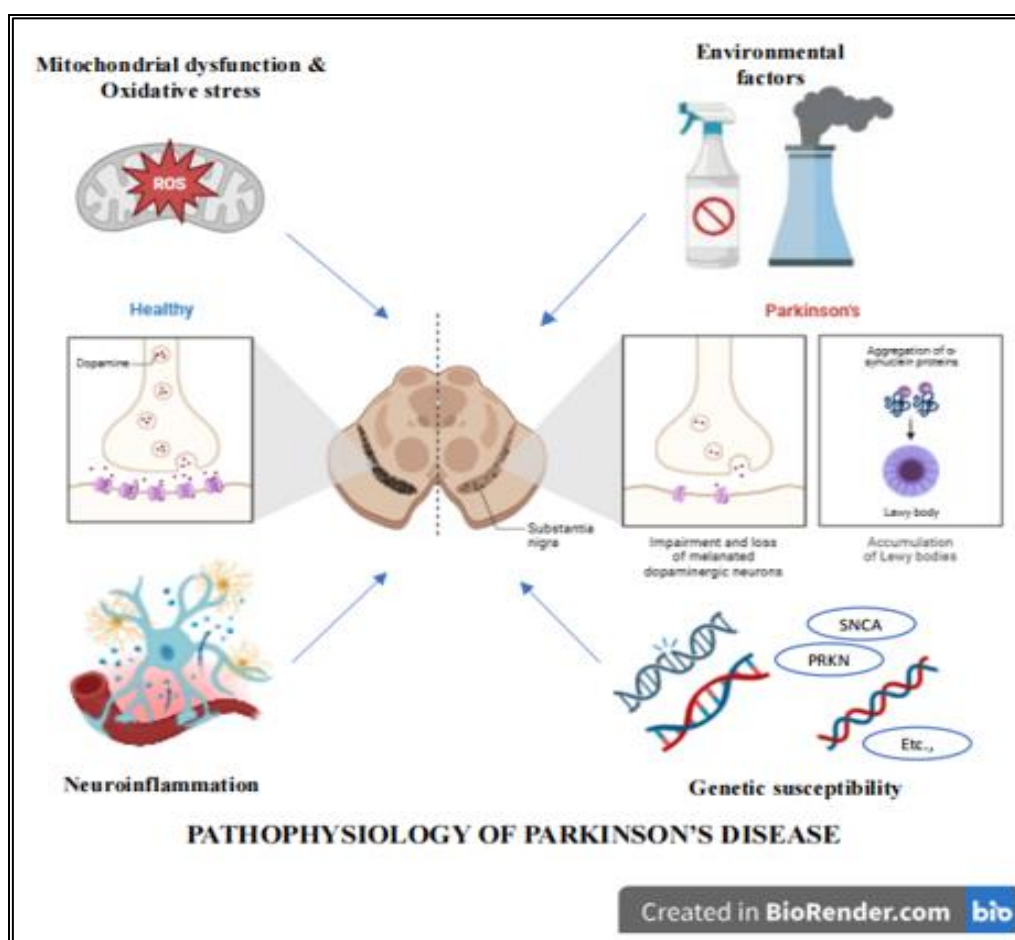


Fig 1 Pathophysiology of Parkinson's Disease

Parkinson's disease is a progressive neurodegenerative disorder characterised primarily by the degeneration of dopaminergic neurons in specific regions of the brain. The disease results from complex interactions between genetic susceptibility, environmental factors, mitochondrial impairment, oxidative stress, and chronic neuroinflammation. These pathological processes ultimately lead to neuronal dysfunction and the development of the characteristic motor symptoms of Parkinson's disease, including tremor, rigidity, bradykinesia, and postural instability.

➤ *Dopaminergic Neuron Degeneration*

One of the hallmark features of Parkinson's disease is the progressive loss of dopaminergic neurons located in the Substantia nigra, particularly in the pars compacta region. These neurons project to the Striatum, forming the nigrostriatal pathway that regulates motor control. Degeneration of these neurons leads to a significant reduction in dopamine levels in the striatum, disrupting normal motor signalling pathways. As dopamine deficiency worsens, patients develop the classical motor symptoms associated with Parkinson's disease. The mechanisms underlying dopaminergic neuronal loss involve oxidative stress, mitochondrial dysfunction, protein misfolding, and neuroinflammatory processes.

➤ *Oxidative Stress*

Oxidative stress plays a critical role in the pathogenesis of Parkinson's disease. It occurs when the production of reactive oxygen species (ROS) exceeds the capacity of cellular antioxidant defence systems. Dopaminergic neurons are particularly vulnerable to oxidative damage due to dopamine metabolism, which generates free radicals and toxic intermediates. Elevated ROS levels can damage cellular components, including lipids, proteins, and DNA, ultimately leading to neuronal dysfunction and death. Additionally, impaired antioxidant mechanisms further exacerbate oxidative injury in the Parkinsonian brain.

➤ *Neuroinflammation*

Chronic neuroinflammation is another important contributor to Parkinson's disease progression. In response to neuronal injury, immune cells in the brain known as microglia become activated and release pro-inflammatory mediators. These include cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6). Persistent activation of microglia creates a toxic inflammatory environment that accelerates neuronal degeneration. This sustained inflammatory response further amplifies oxidative stress and mitochondrial dysfunction, creating a vicious cycle that contributes to disease progression.

➤ *Mitochondrial Dysfunction*

Mitochondria are essential for cellular energy production and neuronal survival. In Parkinson's disease, mitochondrial dysfunction leads to impaired ATP production and increased generation of reactive oxygen species. Dysfunction of mitochondrial complex I in the electron

transport chain has been widely reported in Parkinsonian patients and experimental models. This impairment results in energy failure, increased oxidative stress, and activation of apoptotic pathways that ultimately cause neuronal death. Because dopaminergic neurons require high energy for neurotransmission, mitochondrial impairment significantly increases their vulnerability.

➤ *Protein Aggregation*

Another pathological hallmark of Parkinson's disease is the abnormal aggregation of the protein Alpha-synuclein. Misfolded α -synuclein accumulates within neurons to form intracellular inclusions known as Lewy bodies. These aggregates disrupt normal cellular functions, impair synaptic transmission, and interfere with protein degradation pathways. Accumulation of α -synuclein also promotes mitochondrial dysfunction and triggers inflammatory responses. The progressive spread of α -synuclein pathology throughout the brain is believed to contribute significantly to the neurodegenerative process in Parkinson's disease.

➤ *Mitochondrial Dysfunction and Neurodegeneration*

Mitochondrial malfunction is a leading cause of dopaminergic neuronal degeneration. It is caused by abnormal α -syn and toxins that impede complex I of the electron transport chain [11]. In sporadic Parkinson's disease, dysfunctional complex I has been found in brain samples. In familial early-onset Parkinson's disease, mutations in the autosomal recessive genes Pink1 and Parkin have been linked to impaired mitophagy and mitochondrial quality control [12].

The PINK1/Parkin pathway's involvement in maintaining mitochondrial quality control has been extensively studied [13], with implications for Parkinson's disease pathogenesis and treatment development [14]. The PINK1-mediated activation of Parkin model suggests that a loss in mitochondrial membrane potential causes PINK1 to stabilise at the outer mitochondrial membrane (OMM) and phosphorylate a pre-existing ubiquitin (Ub) residue at serine 65 (Phospho-serine65Ub) [15]. This event recruits auto-inhibited cytosolic Parkin to PINK1 sites and binds the Parkin domain's ring finger protein 1 to pSer65Ub, causing conformational alterations at the OMM level [16]. Parkin is inactive while linked to pSer65-Ub, but activates when PINK1 phosphorylates its Ub-like domain [17]. pSer65Ub plays a crucial role in PINK1 activation, leading to active mitophagy and recruitment of Parkin via a feedforward process. Parkin activates a PINK1 ubiquitin phosphorylation cascade on OMM proteins, leading to the recruitment of more Parkin. A series of events leads to a large activation of the Ub chain assembly [18]. PD patients had higher amounts of pSer65Ub in their postmortem brains, whereas familial forms of PD with Pink1/Parkin mutations have lower levels, highlighting the importance of this route in neurodegeneration [19,20]. Mutations in the SNCA and LRRK2 genes have been linked to mitochondrial dysfunction in PD. LRRK2, a broadly expressed multidomain kinase, regulates mitophagy in iPSC-derived dopamine neurones by removing the OMM adaptor protein MIRO from the MIRO/MILTON/KINESIN motor complex.

This action inhibits mitochondrial transport along the cytoskeleton and autophagosome engulfment, promoting organelle clearance [21]. A G2019S mutation in the kinase domain of LRRK2 inhibits mitophagy initiation [21]. Mitochondrial trafficking has been observed in rat neurones with LRRK2-R1441C mutations [22] as well as neuronal preparations from individuals with idiopathic Parkinson's disease, supporting this hypothesis. Mitophagy dysfunction has a role in Parkinson's disease pathogenesis [21]. Mutant LRRK2 can impair PINK1/Parkin-dependent mitophagy through several pathways [23, 24]. Increased kinase activity in LRRK2-G2019S mutants disrupts protein-protein interactions in the OMM during the PINK1/Parkin-dependent mitophagy pathway [23]. LRRK2-G2019S and R1441C mutations impair PINK1/Parkin-dependent mitophagy via increasing RAB10 phosphorylation, which regulates intracellular membrane trafficking. This event limits RAB10's interaction with optineurin, reducing the accumulation of PINK1/Parkin on depolarised mitochondria [24]. A Mutation in the CHCHD2 gene, which regulates mitochondrial activity, has been discovered as a new risk factor for familial Parkinson's disease (PD). CHCHD2 proteins are important in maintaining mitochondrial cristae [25]. OPA1 stabiliser promotes mitochondrial fusion and accumulates in injured mitochondria [26]. Mutations in CHCHD2 cause intermembrane gap protein precipitation and cytochrome C destabilisation, leading to decreased mitochondrial bioenergetics and increased ROS production [26, 27]. CHCHD2 mutations have been linked to aggregation and oligomerisation of α -synuclein in postmortem brain tissues of individuals with Parkinson's disease and iPSC-derived dopaminergic neurones [28]. Mutations in LRRK2 and CHCHD2 have been linked to mitochondrial homeostasis, although their involvement in causing mitochondrial dysfunction through abnormal mitophagy requires further exploration.

III. INCRETIN HORMONES AND BRAIN FUNCTION

➤ GLP-1 Signalling:

GLP-1R activation prevents pro-inflammatory cytokine production and astrocyte transition to a neurotoxic (A1) phenotype, both of which contribute to Parkinson's neurodegeneration [29]. Research indicates that GLP-1R agonists can reduce inflammation and promote neuroprotection in Parkinson's disease models (both in vitro and in animals). GLP1R agonists have been demonstrated to prevent dopamine neuronal degeneration in many experiments using toxin-induced nigrostriatal degeneration, leading to enhanced motor performance [30-34]. A new GLP-1R agonist, NLY01 (Neuraly, Germantown, MD), was discovered to prevent neurodegeneration and improve behavioural impairments in a mouse model of Parkinson's disease [35]. In a spontaneous PD model with produced α -synuclein fibrils, NLY01 blocked astrocyte transformation, maintained dopaminergic neurones, and improved behavioural impairments [36]. At the molecular level, GLP-1R activation can disrupt inflammatory pathways. Elevated cAMP inhibits NF- κ B activation in immune cells, leading to reduced transcription of inflammatory genes. Upregulation

of neurotrophic factors helps resolve inflammation. Exendin-4 promotes the production of BDNF, a protein that aids in synaptic repair and neuronal survival [37,38]. This study shows that GLP-1 signalling through immunomodulation can reduce chronic neuroinflammation, which causes dopaminergic neurone damage in Parkinson's disease.

➤ GIP Signalling:

Recently, there has been growing interest in the role of Glucose-Dependent Insulinotropic Polypeptide (GIP) signaling in safeguarding the brain against neurodegenerative conditions like Parkinson's disease. GIP, a hormone released by the intestine following food consumption, is primarily recognised for its function in glucose metabolism regulation. However, new research has identified GIP receptors in various parts of the central nervous system, indicating that this hormone might also impact brain activity [39,40]. When GIP attaches to its receptor in the brain, it triggers signalling pathways such as cAMP/PKA and PI3K/Akt pathways that promote neuronal survival and maintain normal cellular operations [39]. These pathways contribute to reducing oxidative stress, lowering inflammation, and enhancing mitochondrial function. Such protective actions are crucial in Parkinson's disease, characterized by the gradual loss of dopaminergic neurons in the Substantia nigra. Additionally, recent studies suggest that therapies targeting incretin hormones could provide enhanced neuroprotective effects when multiple receptors are engaged. Medications like Tirzepatide and Retatrutide activate both GLP-1 and GIP signaling pathways, potentially amplifying their protective impact on the brain [40,42]. By mitigating inflammation, optimizing cellular energy balance, and fostering neuronal survival, GIP signaling might play a significant role in decelerating the progression of Parkinson's disease.

➤ Glucagon Signalling:

Glucagon is a peptide hormone that plays a crucial role in glucose metabolism by activating the glucagon receptor (GCGR), a type of G-protein-coupled receptor that triggers the cAMP-PKA signaling pathway. In addition to its metabolic functions, glucagon signaling is believed to affect neuronal energy balance and survival in neurodegenerative diseases like Parkinson's disease [43]. When GCGR is activated, it raises intracellular cAMP levels, which in turn activates protein kinase A (PKA) and regulates transcription through CREB [44]. These signaling pathways may improve mitochondrial function, boost ATP production, and decrease oxidative stress in neurons [45].

Given that mitochondrial dysfunction and persistent neuroinflammation are major contributors to the degeneration of dopaminergic neurons in the Substantia nigra, adjusting glucagon signaling could support neuronal metabolic stability and survival [46]. Furthermore, activating the glucagon receptor might work in tandem with incretin-based mechanisms used in metabolic-neuroprotective treatments, such as multi-agonist drugs like Retatrutide, which target GLP-1, GIP, and glucagon pathways [47]. Collectively, these effects imply that glucagon signaling might aid in neuroprotection by

enhancing cellular energy metabolism and alleviating neurodegenerative stress in PD.

➤ *Incretin-Based Therapies in Parkinson's Disease*

Incretin hormones are gaining attention for their roles beyond metabolic processes, particularly in safeguarding neuronal functions. These hormones have receptors that are extensively present in the central nervous system, including areas crucial for motor control and neuron survival. This has sparked interest in exploring incretin-based therapies as potential treatments for neurodegenerative diseases like Parkinson's disease. Such therapies might offer neuroprotective benefits by mitigating neuroinflammation, reducing oxidative stress, and enhancing mitochondrial function, which are all critical mechanisms in Parkinsonian neurodegeneration [45,48].

• *GLP-1 Receptor Agonists*

Agonists that target Glucagon-Like Peptide-1 receptor signaling have been thoroughly investigated for their potential to protect neurons. Medications like Semaglutide activate GLP-1 receptors in the brain, initiating intracellular signaling pathways that support neuron survival. Research has demonstrated that GLP-1 receptor agonists can lessen inflammation, minimize oxidative damage, and boost mitochondrial function in neuronal cells [43]. In Parkinson's disease models, these agents have shown the ability to protect dopaminergic neurons and enhance motor function, indicating their promise as disease-modifying treatments [45].

• *Dual Incretin Agonists*

To improve therapeutic outcomes, newer incretin medications have been developed to target multiple receptors at once. Tirzepatide is one such example, activating both GLP-1 and Glucose-Dependent Insulinotropic Polypeptide signaling receptors. Dual receptor activation might offer stronger neuroprotective effects by enhancing neuronal energy metabolism and reducing oxidative stress and inflammation [42,43]. These combined effects could help shield neurons from degeneration and slow the progression of neurodegenerative diseases.

Table 1 Several incretin-based medicines activate different numbers of receptors. Semaglutide and Exenatide exclusively activate the GLP-1 receptor. Tirzepatide stimulates both the GLP-1 and the GIP receptors. In contrast, Retatrutide stimulates three receptors—GLP-1, GIP, and the Glucagon receptor—resulting in greater metabolic effects.

Drug	Receptors activated
Semaglutide	GLP-1 only
Exenatide	GLP-1 only
Tirzepatide	GLP-1 +GIP
Retatrutide	GLP-1+GIP+Glucagon

➤ *Receptor Targets*

The GLP-1 receptor is found in pancreatic β -cells and other parts of the central nervous system. Activation of this receptor increases insulin secretion, glucose metabolism, and neuronal survival. GLP-1 receptor signalling in the brain has been connected with reduced neuroinflammation, decreased oxidative stress, and the protection of

• *Evidence of Neuroprotection*

An increasing number of experimental studies support the neuroprotective potential of incretin-based therapies in Parkinson's disease. In animal models, incretin receptor agonists have been shown to reduce the loss of dopaminergic neurons in the Substantia nigra, a key pathological feature of the disease [41,49]. These treatments also diminish inflammatory responses and enhance mitochondrial function, contributing to neuron survival. The encouraging results observed with GLP-1 and dual incretin agonists have led to the development of next-generation therapies like Retatrutide, which activates GLP-1, GIP, and glucagon receptors simultaneously. By targeting multiple metabolic and neuroprotective pathways, Retatrutide may offer enhanced therapeutic benefits and represents a promising candidate for future research in Parkinson's disease treatment [42,47].

IV. PHARMACOLOGY OF RETATRUTIDE

➤ *Chemical Structure and Design*

The molecular configuration of Retatrutide, emphasising its peptide backbone, specific amino acid modifications, and a linked fatty acid side chain. This fatty acid component enables reversible binding to serum albumin, thereby prolonging the drug's half-life and enhancing its metabolic stability. These structural modifications improve receptor affinity and contribute to its role as a long-acting therapeutic agent. Retatrutide interacts with three primary receptors: the GLP-1 receptor, GIP receptor, and glucagon receptor. These receptors are part of the G protein-coupled receptor (GPCR) family, characterised by seven transmembrane helices and extracellular loops. When Retatrutide binds to these receptors, it triggers downstream intracellular signalling pathways that play a role in glucose homeostasis, energy regulation, and cell survival.

By activating all three receptors simultaneously, Retatrutide acts as a triple incretin receptor agonist, potentially providing enhanced metabolic advantages along with promising neuroprotective effects.

dopaminergic neurons, which are gradually lost in Parkinson's disease [50-52].

The GIP receptor plays an important role in glucose homeostasis by stimulating insulin secretion in response to nutrient intake. In addition to its metabolic functions, GIP receptor activation in the brain can enhance neuronal survival and synaptic plasticity. Experimental studies

suggest that GIP signaling may reduce oxidative stress and neuroinflammatory responses, thereby contributing to neuroprotection in neurodegenerative conditions [52,54]

The glucagon receptor controls glucose and energy metabolism by promoting hepatic glucose synthesis and lipid metabolism. The activation of the glucagon receptor promotes energy expenditure and improves metabolic balance. When paired with GIP and GLP-1 receptor activation, glucagon receptor signalling may boost overall metabolic control and promote cellular energy balance, which is critical for sustaining neuronal function and survival [51,54].

➤ Pharmacokinetics

Retatrutide is a long-acting peptide that may be administered subcutaneously once a week. Following injection, it is progressively absorbed into the systemic circulation, reaching peak plasma concentrations in a few hours. The medication has a long half-life of around 6-7 days, allowing for continuous receptor activation and simple weekly dosage [47,55].

Retatrutide is structurally modified with a fatty acid side chain, allowing for reversible binding to serum albumin. This albumin binding reduces renal clearance and enzymatic breakdown, increasing the drug's circulation half-life [47,56]. Retatrutide, a peptide-based therapy, is predominantly metabolised by proteolytic breakdown into smaller peptides and amino acids rather than hepatic cytochrome P450 pathways [55]. The metabolites are then removed mostly by renal and metabolic mechanisms.

Retatrutide's pharmacokinetic profile shows dose-dependent exposure and predictable accumulation over

repeated weekly dosing, with steady-state concentrations often reached after several weeks of therapy [47,55].

➤ Pharmacodynamics

Retatrutide is a triple-receptor agonist that stimulates the GLP-1, GIP, and glucagon receptors concurrently, resulting in coordinated metabolic and cellular effects [56,43].

Activation of the GLP-1 receptor increases glucose-dependent insulin secretion, inhibits glucagon release, delays stomach emptying, and induces satiety. In addition to its metabolic benefits, GLP-1 receptor signalling has been linked to neuroprotective processes such as reduced oxidative stress, decreased neuroinflammation, and increased neuronal survival[43].

Stimulation of the GIP receptor enhances insulin secretion while also supporting energy metabolism and neural signalling, resulting in enhanced metabolic balance and possible neuroprotective benefits [56]. The activation of the glucagon receptor promotes energy expenditure, lipid metabolism, and hepatic glucose synthesis. When paired with GLP-1 and GIP receptor signalling, glucagon receptor activation improves overall metabolic control and promotes energy balance [56,57]. The activation of these three receptors together has synergistic metabolic and cellular benefits, such as better glucose management, increased energy expenditure, and regulation of inflammation and oxidative stress pathways. These pathways are especially important in disorders characterised by metabolic inefficiency and neurodegeneration, such as Parkinson's disease [43, 57].

V. MECHANISM OF RETATRUTIDE IN PARKINSON'S DISEASE

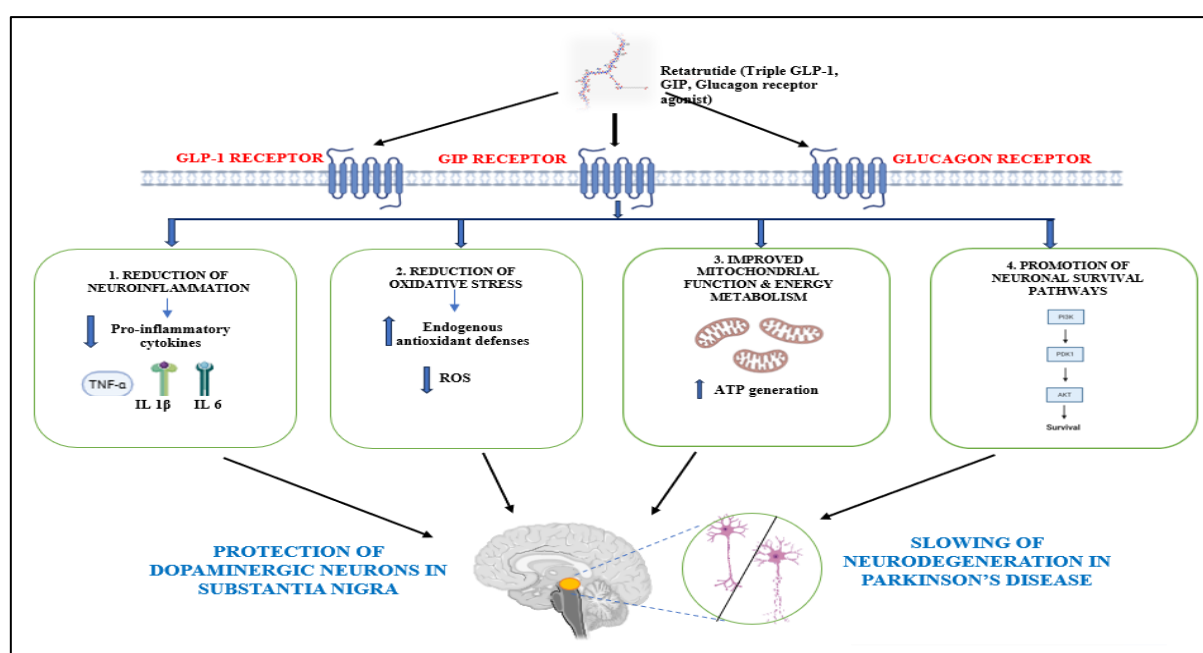


Fig 2 Mechanism of Retatrutide in Parkinson's Disease

Source: Created in Biorender

Retatrutide, a triple agonist of the GLP-1, GIP, and glucagon receptors, may have neuroprotective benefits in Parkinson's disease via a variety of interrelated pathways [45,48,55]. Activating incretin receptors reduces neuroinflammation by reducing pro-inflammatory cytokines such TNF- α , IL-1 β , and IL-6 (2, 4). Retatrutide may also reduce oxidative stress by increasing endogenous antioxidant defences and lowering reactive oxygen species production [48,52]. Furthermore, the medication may increase mitochondrial function and cellular energy metabolism, boosting ATP generation while preserving neuronal survival (5,6). Retatrutide-mediated stimulation of intracellular survival pathways, notably the PI3K/Akt signalling cascade, promotes neuronal survival while inhibiting apoptosis [48,53]. Together, these processes may help protect dopaminergic neurones in the substantia nigra, thereby slowing neurodegeneration in Parkinson's disease [52,53].

➤ *Preclinical Evidence*

Preclinical research on incretin-based therapies has shed light on the potential neuroprotective benefits of Retatrutide for Parkinson's disease. While direct studies involving Retatrutide in Parkinson's disease models are still scarce, investigations into GLP-1 and dual GLP-1/GIP receptor agonists, which operate through similar mechanisms, have shown encouraging neuroprotective results in both cellular and animal models of Parkinson's disease [48,52].

In toxin-induced models like those using MPTP and rotenone to simulate Parkinsonian conditions, incretin receptor agonists have been found to mitigate the loss of dopaminergic neurons in the substantia nigra and enhance motor abilities [45]. These compounds also reduce neuroinflammation by lowering pro-inflammatory cytokines and preventing microglial activation, thus minimizing neuronal damage [52,58].

Moreover, preclinical findings indicate that incretin-based medications can alleviate oxidative stress, boost mitochondrial function, and trigger intracellular survival pathways such as the PI3K/Akt signaling pathway, which promotes neuronal survival and inhibits apoptosis [52,53]. These combined effects help preserve dopaminergic neurons and enhance neuronal function.

Since Retatrutide activates GLP-1, GIP, and glucagon receptors, it is anticipated to deliver similar or even superior neuroprotective effects compared to previous incretin therapies. Consequently, Retatrutide emerges as a promising candidate for further exploration in preclinical and clinical studies aimed at Parkinson's disease.

VI. POTENTIAL CLINICAL APPLICATIONS

➤ *Potential for Disease Modification*

Retatrutide might serve as a disease-modifying treatment for Parkinson's disease by addressing critical pathological mechanisms like neuroinflammation, oxidative

stress, and mitochondrial dysfunction, which are involved in the degeneration of dopaminergic neurons [59].

➤ *Integration with Current PD Therapies*

Retatrutide can potentially be combined with standard treatments such as Levodopa and Carbidopa. While these medications primarily alleviate motor symptoms, Retatrutide might offer additional neuroprotective benefits, possibly improving overall therapeutic results [58].

➤ *Advantages for Metabolic Comorbidities*

Retatrutide has demonstrated positive effects on glucose control, weight loss, and metabolic equilibrium, which could be beneficial for Parkinson's disease patients who also suffer from metabolic issues like obesity or type 2 diabetes [60,61].

VII. CHALLENGES AND LIMITATIONS

• *Limited Clinical Trials in Neurodegenerative Diseases*

While Retatrutide has demonstrated encouraging metabolic effects in clinical trials focused on obesity and metabolic disorders, its potential use in neurodegenerative diseases like Parkinson's disease has not been thoroughly investigated [60,62]. The majority of existing evidence on neuroprotective benefits is derived from studies on incretin-based therapies such as Exenatide and Semaglutide, which target the GLP-1 receptor pathway [45,63]. In contrast, Retatrutide, a triple agonist that acts on GLP-1, GIP, and glucagon receptors, has yet to undergo extensive evaluation in preclinical or clinical models of Parkinson's disease [60,62]. Consequently, comprehensive experimental studies and well-structured clinical trials are essential to assess its effectiveness in slowing neurodegeneration and enhancing motor or cognitive outcomes in PD patients.

• *Safety Considerations*

Another significant limitation pertains to the safety profile of Retatrutide when applied to neurological conditions. Although initial trials in metabolic diseases suggest acceptable tolerability, common side effects such as nausea, vomiting, gastrointestinal discomfort, and appetite changes have been observed [60,64]. Moreover, activation of the glucagon receptor may affect glucose metabolism and energy balance, potentially causing metabolic disturbances in some individuals [57]. Long-term safety data remain limited, especially concerning chronic use in patients with neurodegenerative disorders. Future studies will need to carefully monitor metabolic parameters, cardiovascular effects, and neurological outcomes.

• *Translational Challenges*

Translating findings from metabolic disease studies to neurodegenerative disorders involves several challenges. Firstly, the ability of Retatrutide to effectively cross the blood-brain barrier and exert direct neuroprotective effects in the central nervous system is not yet fully understood [65]. Secondly, animal models of Parkinson's disease may not fully replicate the complex pathology seen in human patients, including progressive dopaminergic neuron loss, protein aggregation, and neuroinflammation [66].

Additionally, determining optimal dosing regimens and treatment duration for neurological benefits may differ from those used in metabolic disorders. These translational gaps underscore the need for integrated preclinical and clinical research to validate Retatrutide as a potential therapeutic strategy for Parkinson's disease.

VIII. FUTURE PERSPECTIVES

The potential of Retatrutide as a treatment for Parkinson's disease suggests several key areas for future investigation. A primary focus should be on conducting well-structured preclinical and clinical trials to assess its effectiveness and safety in neurodegenerative contexts [60,62]. Although current metabolic study findings are encouraging, specific trials in Parkinson's disease are crucial to evaluate its capacity to slow disease progression, safeguard dopaminergic neurons, and enhance both motor and non-motor symptoms [67].

Another promising field is the creation of personalized metabolic therapies. With increasing awareness of metabolic dysfunction and insulin resistance in Parkinson's disease, targeting metabolic pathways could provide therapeutic advantages tailored to individual patients [68,69]. Customizing incretin-based treatments according to personal metabolic profiles, disease stages, and genetic factors might improve treatment outcomes and reduce side effects.

Additionally, the advancement of next-generation incretin-based medications offers a hopeful path. Multi-receptor agonists with better brain penetration, increased receptor selectivity, and optimized pharmacokinetic properties could deliver superior neuroprotective effects [70,71]. Drug design innovations might also aim to minimize side effects while maximizing anti-inflammatory, mitochondrial, and neurotrophic benefits.

In summary, combining metabolic and neurodegenerative research could lead to groundbreaking disease-modifying therapies, positioning incretin-based strategies as a novel approach in managing Parkinson's disease.

IX. CONCLUSION

In conclusion, accumulating evidence indicates that therapies based on incretin have substantial neuroprotective potential in neurodegenerative diseases like Parkinson's disease. Engaging incretin receptors, such as the GLP-1 receptor, GIP receptor, and Glucagon receptor, has been demonstrated to decrease neuroinflammation, mitigate oxidative stress, enhance mitochondrial function, and support neuronal survival. These actions specifically address critical pathological processes involved in dopaminergic neurodegeneration.

Focusing on metabolic pathways is emerging as a promising approach in treating Parkinson's disease. Given that metabolic dysfunction, disrupted energy balance, and mitochondrial impairments are pivotal in disease

progression, therapies that restore these pathways might offer advantages beyond mere symptom relief and could potentially decelerate disease progression.

In this regard, Retatrutide emerges as a novel and advanced therapeutic candidate. By concurrently activating GLP-1, GIP, and glucagon receptors, Retatrutide offers a multi-target strategy that may amplify neuroprotective effects compared to single- or dual-incretin therapies. Although current evidence is primarily derived from preclinical and metabolic studies, further research and clinical trials are crucial to thoroughly assess its efficacy and safety in Parkinson's disease. Overall, Retatrutide shows significant promise as a next-generation therapeutic strategy for neurodegenerative disorders.

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