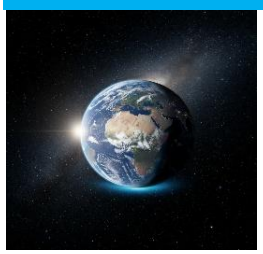
Quality in Sport. 2026;51:68253. eISSN 2450-3118.

https://doi.org/10.12775/QS.2026.51.68253



Quality in Sport. eISSN 2450-3118

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CHMIEL, Gabriela, BACHURSKI, Patryk, KALINOWSKI, Paweł, MIĘDLAR, Maja, MUDA, Martyna, PACEK, Szymon, PIERZGA, Elisabetta, WIŚNIEWSKI, Karol Paweł, WITKOWSKI, Paweł and ZARAŃSKI, Bartosz. Neuroprotective Mechanisms of GLP-1 Pathway Activation in Parkinson's Disease - Foundations For Future Disease-Modifying Strategies. Quality in Sport. 2026;51:68253. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.51.68253

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 14.01.2026. Revised: 31.01.2026. Accepted: 31.01.2026. Published: 05.02.2026.

Neuroprotective Mechanisms of GLP-1 Pathway Activation in Parkinson's Disease - Foundations For Future Disease-Modifying Strategies

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Abstract

Introduction and Purpose

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the selective loss of dopaminergic neurons, accumulation of α-synuclein, mitochondrial dysfunction, neuroinflammation, and systemic metabolic disturbances. While current therapies effectively address motor symptoms, interventions capable of modifying disease progression remain lacking. In recent years, activation of the glucagon-like peptide-1 (GLP-1) signaling pathway has emerged as a promising neuroprotective strategy in PD. This review focuses on literature published from 2021 onwards, synthesizing mechanistic insights into GLP-1 receptor agonists (GLP-1RAs), dual GLP-1/GIP agonists, and GLP-1-based microbiome interventions, with an emphasis on their potential to act as disease-modifying therapies by targeting the core pathophysiological processes underlying PD. Given the recent failure of several α-synuclein-targeted monotherapies, GLP-1 pathway activation offers a systems-level alternative capable of addressing multiple convergent drivers of neurodegeneration

Materials and Methods

A narrative, mechanism-focused review was conducted including experimental, translational, and clinical studies published since 2021. A structured PubMed search was performed using relevant keywords and MeSH terms related to Parkinson's disease, mitochondrial dysfunction, neuroinflammation, autophagy, α-synuclein, insulin/metabolic signaling, and GLP-1 receptor agonists. Studies were evaluated across key pathogenic axes of Parkinson's disease, including mitochondrial and oxidative stress pathways, glial-mediated neuroinflammation, α-synuclein proteostasis, synaptic and circuit-level dysfunction, and metabolic signaling. Evidence was drawn from toxin-based, genetic, synucleinopathy, and PD–diabetes comorbidity models, as well as clinical trials and meta-analyses, with priority given to studies providing mechanistic insight.

Results

Across diverse models of Parkinson's disease, activation of the GLP-1 pathway consistently enhanced mitochondrial quality control by promoting mitophagy, stimulating PGC-1α–dependent biogenesis and restoring fission–fusion balance, while concurrently reducing oxidative stress. GLP-1 receptor agonists and dual GLP-1/GIP agonists suppressed microglial and astrocytic activation, inhibited NF-κB and NLRP3 inflammasome signaling and limited necroptotic as well as ferroptotic cell death. Multiple agents also normalized autophagic flux and ER–mitochondrial crosstalk, reduced α-synuclein accumulation, and, in certain models, attenuated prion-like propagation of α-synuclein. Sustained GLP-1 signaling preserved dopaminergic synaptic transmission, substantia nigra pars compacta firing patterns, and motor behavior. Importantly, these therapies restored neuronal insulin/IGF signaling and improved systemic metabolic parameters, highlighting the integration of peripheral and central neuroprotective effects. Clinical and meta-analytic evidence further supports the safety of GLP-1RAs and demonstrates meaningful improvements in motor function, although definitive proof of disease-modifying efficacy remains to be established.

Conclusion
The latest post-2021 studies support GLP-1 pathway activation as a multi-dimensional neuroprotective strategy in Parkinson's disease, concurrently addressing mitochondrial dysfunction, neuroinflammation, impaired proteostasis, synaptic failure and metabolic dysregulation. Distinct GLP-1-based interventions display partially divergent mechanistic profiles, offering the potential for tailored application according to disease stage or patient subgroup. To determine whether these convergent mechanisms translate into genuine disease-modifying effects, future clinical trials should be adequately powered, biomarker-anchored and focused particularly on early or prodromal stages of PD.
Key Words: Parkinson's disease, GLP-1 receptor agonists, dual GLP-1/GIP agonists, GLP-1–secreting probiotics, neuroprotection, mitochondrial dysfunction, oxidative stress, neuroinflammation, glial activation, autophagy, α-synuclein, proteostasis, ER stress, synaptic function, basal ganglia circuits, insulin resistance, metabolic dysregulation, disease modification.

Introduction

Parkinson's disease (PD) is a complex, multifactorial neurodegenerative disorder characterized primarily by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to marked depletion of dopamine within the striatum and subsequent dysfunction of basal ganglia circuits. A central neuropathological hallmark of PD is the misfolding, aggregation, and abnormal accumulation of α-synuclein, which forms Lewy bodies and Lewy neurites and spreads through vulnerable neuronal networks in a stereotyped pattern. These molecular and cellular changes disrupt synaptic transmission, mitochondrial function, proteostasis, and neuroinflammatory homeostasis, ultimately contributing to neuronal dysfunction and death.

Clinically, this core pathology manifests as the cardinal motor symptoms of PD, including bradykinesia, resting tremor, muscular rigidity, and postural instability. However, PD is increasingly recognized as a systemic disorder with a broad spectrum of non-motor symptoms that may precede motor onset by years or even decades. These include cognitive impairment and dementia, depression and anxiety, apathy, autonomic disturbances such as orthostatic hypotension and gastrointestinal dysfunction, sensory abnormalities, and sleep disorders such as rapid eye movement (REM) sleep behavior disorder. Non-motor symptoms often contribute substantially to reduced quality of life and caregiver burden and may reflect widespread neurodegeneration beyond the nigrostriatal system.

Despite significant advances in symptomatic management most notably dopamine replacement strategies, deep brain stimulation, and adjunct pharmacological therapies current treatments primarily address downstream neurotransmitter deficits rather than the underlying neurodegenerative process. As a result, disease progression continues unabated, with increasing disability over time. Numerous disease-modifying strategies targeting α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, and genetic risk pathways have been investigated in preclinical and clinical studies. However, to date, no therapeutic intervention has conclusively demonstrated robust and reproducible disease-modifying effects in patients. This underscores the urgent need for improved mechanistic understanding of PD pathogenesis, reliable biomarkers for early diagnosis and progression, and innovative therapeutic approaches capable of altering the course of the disease rather than merely alleviating its symptoms.

Over the last decade, glucagon-like peptide-1 receptor agonists (GLP-1RAs), originally developed for type 2 diabetes mellitus, have emerged as promising candidates for disease modification in PD. GLP-1 receptors (GLP-1R) are expressed not only in pancreatic β-cells but also in neurons and glial cells in the substantia nigra, striatum, cortex, and hippocampus, as well as in endothelial and immune cells [1,2]. Activation of GLP-1R engages cAMP/PKA/Epac, PI3K–Akt, and MAPK/ERK pathways and initiates gene expression programs that promote cell survival, mitochondrial biogenesis, antioxidant defense, synaptic maintenance, and metabolic homeostasis [1,3]. These signaling cascades intersect with several mechanistic axes implicated in PD, including mitochondrial dysfunction, oxidative stress, neuroinflammation, impaired proteostasis and α-synuclein handling, synaptic failure, and brain insulin resistance [2,4].

Since 2021, a substantial body of new experimental and translational work has clarified how GLP-1 pathway activation influences these PD-relevant mechanisms. Classic GLP-1RAs such as exendin-4/exenatide, liraglutide, semaglutide, and lixisenatide have been evaluated in toxin-based PD models (MPTP, 6-OHDA, rotenone), demonstrating consistent neuroprotective effects linked to mitochondrial quality control, oxidative stress reduction, and suppression of neuroinflammation [5,6]. Evidence from genetic PD models, including MitoPark and A53T α-syn mice, further supports disease-modifying potential through preservation of dopaminergic neurons and attenuation of α-syn–related pathology [7,8]. In parallel, studies using α-synuclein pre-formed fibril (PFF) models have shown that GLP-1R activation can limit the propagation of pathological α-syn species [9,10]. Dual GLP-1/GIP receptor agonists and GLP-1–secreting engineered bacteria have provided complementary mechanistic insights and in some models, superior neuroprotection compared with single-receptor agonists [8,11]. Clinical syntheses and meta-analyses during this period indicate modest but reproducible motor benefits of GLP-1RAs in PD, while underscoring the need for biomarker-driven trials to establish true disease modification [4,12].

This review aims to provide a detailed, mechanistically oriented synthesis of recent advances in GLP-1 pathway activation in Parkinson's disease, focusing specifically on studies published from 2021 onward. We first delineate the core mechanisms underlying PD pathophysiology alongside central GLP-1 receptor signaling. Building on this foundation, we systematically examine how GLP-1 receptor agonists influence key biological processes, including mitochondrial dynamics and oxidative stress, neuroinflammation and glial function, autophagy and α-synuclein proteostasis, synaptic and neural circuit integrity, and insulin-mediated metabolic pathways. We then provide a comparative evaluation of existing GLP-1–based interventions and highlight how the emerging mechanistic insights can inform the rational design of future disease-modifying therapies.

Mechanisms of PD Relevant to GLP-1R-Based Interventions

Modern views of PD emphasize that it is not solely a disorder of dopamine deficiency but a systems-level pathology arising from the interaction of several partially independent processes [1,2].

Mitochondrial dysfunction and oxidative stress represent central contributors to the pathophysiology of Parkinson's disease. Dopaminergic neurons are particularly vulnerable due to their high energetic demands, autonomous pacemaker activity, and extensive axonal arborization, all of which render them highly dependent on efficient oxidative phosphorylation. These features also increase their susceptibility to damage from reactive oxygen species (ROS). Experimental models have underscored this vulnerability : mitochondrial complex I inhibitors, such as MPTP and rotenone, reproduce many of the cardinal features of PD in animals, including selective dopaminergic neurodegeneration and motor deficits. Beyond acute toxic insults, intrinsic defects in mitochondrial quality control further exacerbate neuronal stress. Impaired mitophagy reduces the clearance of damaged mitochondria, disturbances in the fission–fusion balance compromise mitochondrial network integrity, and deficits in mitochondrial biogenesis limit the replacement of dysfunctional organelles. Together, these processes contribute to a cumulative burden of mitochondrial injury, setting the stage for progressive neuronal dysfunction and degeneration. [5,13]

Neuroinflammation and glial activation provide a second major axis. Activated microglia and reactive astrocytes are abundant in PD brains and in animal models. Microglia can adopt pro-inflammatory phenotypes that produce cytokines such as TNF-α, IL-1β, and IL-6 and generate additional ROS and reactive nitrogen species. Astrocytes, under chronic stress and microglial influence, can become neurotoxic and contribute to disease progression.

Inflammatory signaling pathways such as NF-κB, the NLRP3 inflammasome, and programmed cell death modules including necroptosis and ferroptosis have all been implicated in PD-like conditions [14,15].

Impaired proteostasis and α-synuclein pathology constitute a third axis. Misfolded and aggregated α-synuclein accumulates within neurons and propagates via synaptically connected networks in a prion-like manner. Disruption of the autophagy–lysosome system, chronic ER stress, ER–mitochondrial uncoupling, and chaperone system failure all contribute to inadequate clearance of α-synuclein and other misfolded proteins. Toxin models do not always recapitulate this dimension, but genetic models such as A53T α-synuclein mice, PFF seeding paradigms, and synucleinopathy-based bacterial GLP-1 studies highlight its importance [3,9].

At the network level, synaptic and circuit dysfunction link cellular pathology to clinical manifestations. Degeneration of nigrostriatal dopaminergic neurons disrupts cortico–striato–thalamo–cortical loops that regulate movement, motivation, and aspects of cognition. In addition to outright cell loss, abnormal firing patterns of substantia nigra pars compacta neurons, reduced synaptic dopamine release, and altered plasticity at corticostriatal synapses contribute to PD symptomatology [16,17].

Finally, there is growing recognition that PD is tied to systemic metabolic dysregulation. Epidemiological data indicate that type 2 diabetes mellitus and insulin resistance are associated with increased PD risk and potentially faster progression. Experimental models in which diabetes is combined with PD toxins show exacerbated neurodegeneration, and post-mortem and experimental data reveal impaired insulin and IGF signaling in the PD brain. This has led to the idea that PD may in part reflect a "brain insulin-resistant state," with consequences for mitochondrial function, proteostasis, and synaptic resilience [6,18].

The multifactorial nature of PD pathogenesis makes therapeutic strategies that act on several of these axes simultaneously particularly attractive. Activation of the glucagon-like peptide-1 (GLP-1) signaling pathway has emerged as a strong candidate in this regard, given its capacity to influence mitochondrial function, inflammation, proteostasis, synaptic activity, and metabolic homeostasis in a coordinated manner [1,4].

Central GLP-1 Receptor Signaling and its Mechanistic Relevance

GLP-1 receptors are widely expressed throughout the brain, including in dopaminergic neurons of the substantia nigra pars compacta, striatal and cortical neurons, as well as in glial cells. Activation of GLP-1 receptors by GLP-1 or GLP-1 receptor agonists (GLP-1RAs) engages Gs proteins, leading to increased intracellular cAMP and subsequent activation of PKA and Epac2. In neurons, this cascade promotes phosphorylation and activation of transcription factors such as CREB, which in turn regulate the expression of genes involved in mitochondrial biogenesis (including PGC-1α, NRF1/2, and TFAM), antioxidant defenses (SOD, catalase, glutathione peroxidase), synaptic proteins, and neurotrophic factors. Concurrently, activation of the PI3K–Akt pathway and downstream inhibition of GSK-3β support pro-survival signaling, modulate autophagy via mTOR, and enhance insulin/IGF pathway function. MAPK/ERK signaling further contributes to cellular resilience and synaptic plasticity, collectively reinforcing neuronal survival and functional integrity. [1,2]

GLP-1 receptors are also expressed in microglia, astrocytes, as well as endothelial and immune cells, enabling GLP-1 receptor agonists (GLP-1RAs) to modulate inflammatory and vascular processes relevant to Parkinson's disease pathophysiology. Systemically, GLP-1RAs improve glycemic control, enhance insulin sensitivity, optimize lipid profiles, and reduce peripheral inflammation, effects that may indirectly influence PD-related mechanisms within the brain. [4,12].

Clinically approved GLP-1RAs differ in pharmacokinetics and central nervous system penetration, yet exendin-4/exenatide, liraglutide, semaglutide, and lixisenatide all reach the brain or exert sufficient central activity to modulate neuronal and glial functions. Emerging therapies, including dual GLP-1/GIP agonists (e.g., tirzepatide), long-acting formulations such as the pegylated exendin-4 analog NLY01, and engineered GLP-1–secreting bacteria, provide additional approaches for sustained, low-level activation of the GLP-1 pathway via the gut–brain axis. Recent reviews highlight that GLP-1R activation can correct insulin resistance, mitigate oxidative and excitotoxic stress, modulate neuroinflammation, and enhance proteostasis across models of Parkinson's and Alzheimer's disease. [1,19].

Collectively, these signaling properties indicate that GLP-1 pathway activation has the capacity to target multiple core mechanistic pillars of Parkinson's disease simultaneously, including mitochondrial dysfunction, neuroinflammation, impaired α-synuclein proteostasis, synaptic and circuit-level deficits, and systemic metabolic dysregulation. [2,4].

GLP-1RAs and Mitochondrial/Oxidative Stress Mechanisms in PD

A substantial cluster of recent studies has focused on how GLP-1RAs affect mitochondrial quality control and oxidative stress in PD models. Liraglutide has been particularly prominent in this regard.

GLP-1 receptor agonists, such as liraglutide, exert multifaceted neuroprotective effects in Parkinson's disease models, targeting key mechanisms underlying dopaminergic neuron vulnerability. In MPTP-treated mice, liraglutide has been shown to enhance mitophagy, evidenced by increased expression of PINK1 and Parkin, elevated LC3-II levels, and improved autophagosome–lysosome fusion, indicative of restored mitophagic flux. These effects are accompanied by reductions in mitochondrial reactive oxygen species and cytochrome c release, reflecting stabilization of mitochondrial membrane potential and suppression of apoptosis. Beyond mitochondrial protection, GLP-1RAs modulate neuroinflammatory responses by acting on microglia and astrocytes, attenuating pro-inflammatory cytokine production, and promoting a shift toward neuroprotective glial phenotypes. They also support synaptic and circuit integrity through CREB-mediated upregulation of neurotrophic factors and synaptic proteins, and enhance insulin/IGF signaling, further improving neuronal resilience. Collectively, these actions translate into preservation of nigrostriatal tyrosine hydroxylase expression, maintenance of striatal dopamine content, and improvements in motor function, highlighting the capacity of GLP-1 pathway activation to simultaneously target multiple core pathogenic mechanisms in PD [5].

A 2022 follow-up study further extended this mechanistic framework by examining mitochondrial biogenesis and fission–fusion dynamics. In an MPTP model, liraglutide was shown to upregulate PGC-1α, NRF1/2, and TFAM, restore the balance between mitochondrial fission and fusion through modulation of DRP1, MFN, and OPA1, and normalize mitochondrial morphology. Knockdown experiments indicated that PGC-1α was essential for the full neuroprotective effect of liraglutide. These findings demonstrate that liraglutide regulates the mitochondrial quality control system via PGC-1α, supporting both mitophagy and biogenesis to maintain a healthier mitochondrial population. [13].

Semaglutide provides complementary insights into mitochondrial and oxidative mechanisms. In 2022, studies in 6-OHDA–treated SH-SY5Y cells demonstrated that semaglutide reduced reactive oxygen species, restored mitochondrial membrane potential, and enhanced activities of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase. These improvements were accompanied by increased autophagic flux and reduced α-synuclein accumulation, indicating coordinated regulation of mitochondrial and autophagic pathways under GLP-1 receptor stimulation [6]. In 2025, a rat model combining high-fat diet and

streptozotocin-induced diabetes with rotenone-induced PD showed that semaglutide, alone or in combination with metformin, improved brain antioxidant status, attenuated oxidative–inflammatory biomarkers, and ameliorated motor, cognitive, and olfactory deficits. The same treatment also normalized systemic glucose and lipid parameters, suggesting that improved peripheral metabolism may alleviate central mitochondrial and oxidative stress [18].

Exendin-4, administered as sustained-release PT320, has been evaluated in the MitoPark mouse model, which recapitulates intrinsic mitochondrial dysfunction in dopaminergic neurons. Early, biweekly PT320 treatment improved spontaneous locomotion and motivated behavior, preserved dopaminergic markers, and protected neurotransmission as assessed by fast-scan cyclic voltammetry and PET imaging [16]. Subsequent studies demonstrated that PT320 reduced mitochondrial ROS, inhibited cytochrome c release, and maintained mitochondrial morphology in nigrostriatal neurons, despite continued decline in overall mitochondrial number. These findings suggest that GLP-1 pathway activation enhances mitochondrial quality and resilience even in the context of progressive organelle loss [7].

Lixisenatide, studied in 2025 in α-synuclein preformed fibril models, further exemplifies mitochondrial protection within a synucleinopathy context. Treatment reduced mitochondrial dysfunction, preserved membrane potential, decreased ROS, and limited cytochrome c release and caspase-3 activation in both cells and brain tissue. These mitochondrial benefits were accompanied by reductions in α-synuclein aggregation, decreased propagation of pathology, and preservation of dopaminergic neurons and motor function [9].

Taken together, these studies indicate that GLP-1 receptor activation across different agents reinforces mitochondrial resilience by enhancing mitophagy, promoting PGC-1α–dependent biogenesis, correcting fission–fusion imbalances, reducing ROS, and preventing mitochondrial apoptosis. While the emphasis differs among agents—liraglutide demonstrates detailed mechanistic effects on mitophagy and PGC-1α, semaglutide highlights antioxidant and mitochondrial stabilization linked to autophagy, PT320 emphasizes mitochondrial quality maintenance in a genetic PD model, and lixisenatide integrates mitochondrial protection with α-synuclein pathology containment all converge on the principle that robust mitochondrial support is a central component of GLP-1–mediated neuroprotection in Parkinson’s disease [1,4]. (Fig. 1).

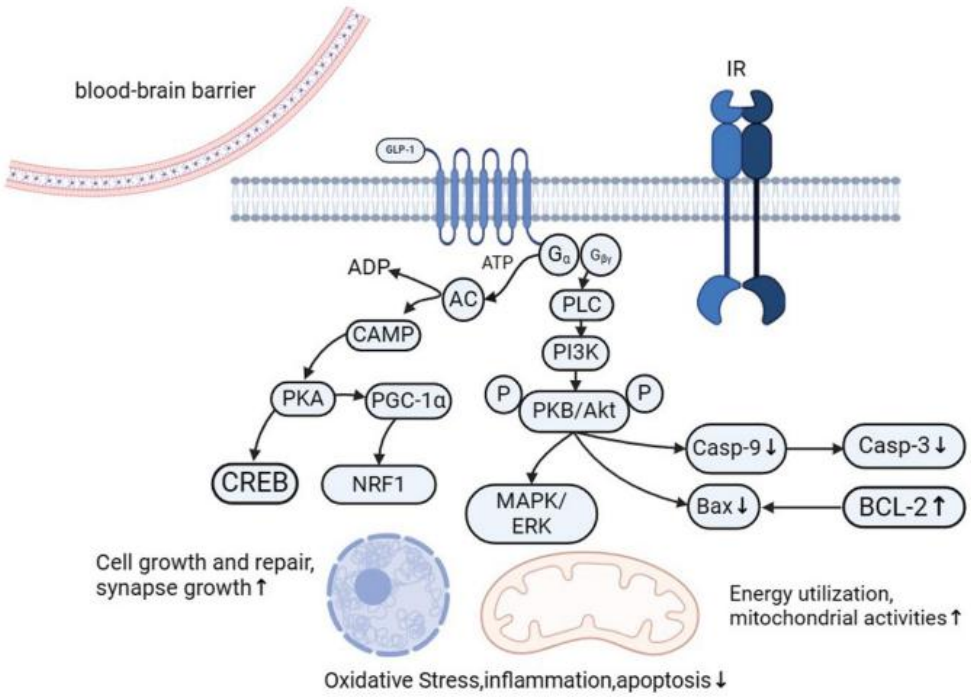


Figure 1. GLP-1 (glucagon-like peptide-1) plays a vital role in neuroprotection and regeneration through multiple mechanisms. It promotes the expression of NGF and BDNF, activates the PI3K/Akt signaling pathway, and reduces neuroinflammation, thereby facilitating nerve regeneration. GLP-1 also enhances mitochondrial activity by activating AMPK, increasing the expression of genes involved in mitochondrial biogenesis, and reducing the activation of mitochondrial apoptotic pathways. It reduces oxidative stress by decreasing ROS production and upregulating antioxidant enzymes. Additionally, GLP1 inhibits the NF-κB signaling pathway and reduces the activation of microglia and astrocytes, thereby mitigating inflammatory responses. Furthermore, GLP-1 significantly decreases cell apoptosis by regulating the expression of Bcl-2 family proteins and inhibiting apoptotic signaling pathways. These combined mechanisms enable GLP-1 to play a vital protective role in maintaining the health and function of the nervous system. [4]

Modulation of Neuroinflammation and Glial Responses by GLP-1 Pathway Activation

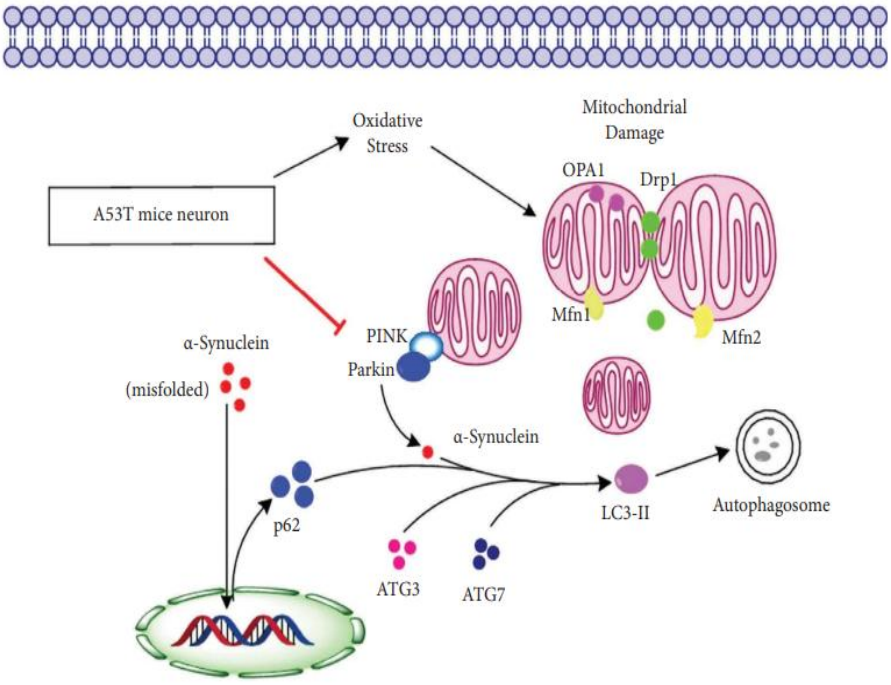
Neuroinflammation is increasingly recognized as a modifiable driver rather than a mere bystander in PD progression. Several recent studies show that GLP-1RAs attenuate microglial and astrocytic pathology and reshape inflammatory signaling in PD models.

Activation of the GLP-1 signaling pathway exerts potent anti-inflammatory effects in Parkinson's disease models. In MPTP-treated mice, liraglutide reduced Iba1-positive microglia and GFAP-positive astrocytes in the substantia nigra and striatum, lowered levels of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6, and engaged key signaling changes such as AMPK activation and NF-κB inhibition. These alterations suggest that GLP-1R activation shifts glial and neuronal gene expression toward a less inflammatory profile while linking energy sensing to inflammation control, concomitant with improvements in motor function [14]. In a model of PD with diabetes comorbidity, liraglutide improved systemic metabolic parameters, reduced necroptosis-related proteins (TNF-α, RIP1) and phosphorylated NF-κB p65 in the brain, and preserved dopaminergic neurons and motor performance, highlighting its ability to mitigate regulated inflammatory cell death under metabolic stress [20].

Exendin-4 has been shown to exert similar effects. In 2022 it was reported that exendin-4 reversed MPTP-induced motor dysfunction, reduced microgliosis and astrogliosis, and protected dopaminergic neurons. They showed that exendin-4 promoted microglial polarization toward an anti-inflammatory phenotype and reduced pro-inflammatory cytokine secretion. In vitro, exendin-4 and linagliptin suppressed activation of the NLRP3 inflammasome in BV2 microglia, thereby directly targeting a major innate immune mechanism linked to PD [21]. More broadly, recent reviews of exendin-4 in PD and Alzheimer's disease emphasize its anti-inflammatory and microglia-modulating actions alongside other neuroprotective pathways [19,22,23].

Engineered GLP-1–secreting bacteria provide a means for chronic, low-level GLP-1 signaling from the gut to modulate both brain and systemic inflammation. In MPTP-treated mice, oral administration of *Escherichia coli* Nissle 1917 engineered to express GLP-1 reduced inflammation in the brain and colon, suppressed microglial and astrocyte activation, improved colonic barrier integrity, partially normalized microbiota composition, and enhanced dopaminergic neuron survival and motor performance. [11]. Work with *Lactococcus lactis* MG1363-pMG36e-GLP-1 provides complementary evidence for microbiome-mediated GLP-1 signaling. In an MPTP mouse model, oral administration of this strain reduced locomotor impairments, protected dopaminergic neurons, suppressed glial activation, downregulated pro-inflammatory mediators, and activated Keap1/Nrf2/GPX4 signaling, thereby preventing ferroptotic cell death. [24]. n 2025, these findings were extended to SncaA53T transgenic mice, where GLP-1–secreting *Lactococcus lactis* reduced pathological α-synuclein aggregation, alleviated motor deficits, suppressed microglial activation and lipopolysaccharide-related inflammatory signaling, and modulated gut dysbiosis. [25]. These studies demonstrate that GLP-1 pathway activation can attenuate neuroinflammation and microglial toxicity even when delivered via the microbiome.

Dual GLP-1/GIP agonists also exhibit potent anti-inflammatory activity. In 2021, the dual agonists DA5-CH and NLY01 were compared in an MPTP model. Both agents improved motor performance and protected dopaminergic neurons, but DA5-CH more effectively reduced



NF-κB activation, decreased pro-inflammatory cytokine levels, and lowered α-synuclein accumulation.[15]. Findings showed that DA5-CH was superior to liraglutide in the A53T α-synuclein transgenic mouse model, with greater reductions in motor deficits, α-synuclein accumulation, and inflammatory markers and more robust dopaminergic protection [8] (Fig. 2).

Figure 2. Overview of the proposed mechanism of clearance of α-synuclein. Autophagy is compromised in the A53T tg mouse model. Activating the GLP-1 and GIP receptors increases autophagy in neurons via CREB signalling, thereby reducing the levels of α-synuclein in the substantia nigra and the striatum. [8]

It was also reported that tirzepatide, another dual GLP-1/GIP agonist, improved locomotion, reduced TNF-α and IL-6, increased striatal dopamine levels, and lowered α-synuclein expression more effectively than exendin-4 in a rotenone model [26]. Reviews of GLP-1 class drugs in PD synthesize these findings and point to dual agonists as particularly promising from an inflammation and neurotrophic standpoint [2,4].

Collectively, these studies establish that activation of the GLP-1 signaling pathway dampens microglial and astrocytic activation, suppresses NF-κB and NLRP3 inflammasome signaling, reduces pro-inflammatory cytokine production, and interferes with regulated inflammatory cell death pathways including necroptosis and ferroptosis. By reshaping the inflammatory milieu toward one that supports neuronal survival, GLP-1-based therapies address a key disease-modifying axis in PD pathogenesis [2,4].

GLP-1 Pathway Effects on Autophagy, ER Stress, and α-Synuclein Proteostasis

A third major mechanistic domain in which GLP-1 pathway activation appears highly relevant to PD is proteostasis, particularly the autophagy–lysosome system, ER stress responses, and α-synuclein handling. Recent work with semaglutide, liraglutide, lixisenatide, engineered probiotics, and dual agonists provides important insights.

Examined semaglutide in 6-OHDA-treated SH-SY5Y neuroblastoma cells and showed that it increases markers of autophagic flux, including LC3-II and Beclin-1, while reducing p62 accumulation. Semaglutide restored lysosomal enzyme expression, decreased α-synuclein accumulation, reduced oxidative stress, and improved cell viability. Liraglutide produced similar but somewhat less pronounced effects. Both drugs activated the IRS-1/Akt/CREB signaling pathway, suggesting that restored insulin/IGF signaling is upstream of autophagy normalization and α-synuclein clearance [6]. In a complementary in vivo study it was reported that semaglutide reduced α-synuclein levels and dopaminergic degeneration and improved motor behavior in a 6-OHDA rat model, reinforcing the view that semaglutide enhances α-synuclein proteostasis under PD-like insults [27].

Lixisenatide focuses on the propagation aspect of α-synuclein biology. One of the scientific reasearches used α-synuclein PFFs to seed pathology in cells and mouse substantia nigra. They found that lixisenatide markedly reduced phosphorylated α-synuclein (Ser129), decreased aggregated α-synuclein species, and limited the spread of PFF-driven pathology across brain regions over a 20-week period. These changes were associated with reduced mitochondrial dysfunction and apoptotic signaling and with preservation of dopaminergic neurons and motor function [9]. This study is notable for directly linking GLP-1R agonism to attenuation of prion-like α-synuclein propagation, a core driver of PD progression.

Exendin-4's impact on autophagy and α-synuclein has also been highlighted in recent literature, although detailed primary mechanistic data come largely from pre-2021 studies. Contemporary reviews summarize that exendin-4 enhances autophagic flux, reduces α-synuclein aggregation,

normalizes ER stress responses, and mitigates proteasome impairment in PD-related models, adding to its mitochondrial and anti-inflammatory profile [1,23].

At the level of fundamental neuronal cell biology, it was examined how incretin mimetics affect the ER–mitochondrial axis and unfolded protein response in LUHMES dopaminergic-like neurons under chronic calcium-dependent ER stress. They found that liraglutide and a dual GLP-1/GIP agonist restored ER–mitochondrial contacts, normalized UPR signaling, increased mitochondrial biogenesis, and enhanced macroautophagy, collectively switching cell fate from death to survival. These effects demonstrate that GLP-1R and GIPR activation can coordinate ER stress resolution, mitochondrial homeostasis, and autophagic clearance, mechanisms that are clearly relevant to α-synuclein and proteotoxic stress in PD [3]. A 2021 conference report from the same group reinforced these conclusions and suggested that similar mechanisms may operate across several neurodegenerative diseases [28].

Engineered probiotics further illustrate proteostatic mechanisms, it was shown that L. lactis MG1363-pMG36e-GLP-1 protects dopaminergic neurons in MPTP mice via activation of the Keap1/Nrf2/GPX4 axis, preventing ferroptotic cell death. This axis modulates lipid peroxidation and iron metabolism, both of which can influence α-synuclein aggregation indirectly [24]. In 2025, they extended this work to SncaA53T transgenic mice, finding reduced pathological α-synuclein aggregation, improved motor behavior, and modulation of gut-derived inflammatory signals and microglial activation [25]. These probiotic interventions, while not using pharmaceutical GLP-1RAs, support the broader concept that GLP-1 signaling stabilizes proteostasis and mitigates α-synuclein pathology across multiple mechanistic layers.

Recent reviews of GLP-1 class drugs in PD and Alzheimer's disease have integrated these findings and proposed that GLP-1 pathway activation should be viewed as a modulatory lever for the autophagy–lysosome system, ER stress responses, and α-synuclein proteostasis, complementing its mitochondrial and anti-inflammatory actions [1,2,4]. Collectively, the new literature supports an integrated model in which GLP-1R activation corrects defective proteostasis by enhancing autophagy and lysosomal function, normalizing ER stress and ER–mitochondrial coupling, reducing α-synuclein burden, and in some cases limiting α-synuclein propagation [1,2,4].

Synaptic and Circuit-Level Effects of GLP-1 Pathway Activation

Beyond cell survival and proteostasis, the ultimate goal of disease-modifying therapy is to sustain or restore functional brain circuits. Several recent studies demonstrate that GLP-1 pathway activation preserves dopaminergic synaptic function and network activity in PD models.

PT320, a sustained-release formulation of exendin-4, has been studied in depth in MitoPark mice. In lately 2023 it was reported that early PT320 treatment preserved dopamine release and reuptake in striatal and nucleus accumbens terminals, as measured by fast-scan cyclic voltammetry, and protected dopaminergic fibers on PET imaging. These functional measures correlated with improved spontaneous locomotion, better performance in motivated tasks, and preservation of dopaminergic markers such as tyrosine hydroxylase. The data indicate that sustained GLP-1R activation can maintain synaptic dopamine transmission in the face of progressive mitochondrial and dopaminergic stress [16]. The 2024 follow-up study showing preservation of mitochondrial morphology and function provides a clear mechanistic underpinning: by stabilizing mitochondria, PT320 sustains synaptic energy supply and prevents loss of release and reuptake capacity [7].

The effects of exendin-4 on the intrinsic firing properties of substantia nigra pars compacta dopaminergic neurons were examined in a chronic low-dose MPTP mouse model. They found that exendin-4 increased the number of spontaneously active nigral dopaminergic neurons and

normalized their firing rates and patterns. These electrophysiological changes aligned with improved motor behavior, implying that GLP-1R activation recalibrates nigral pacemaker activity and, by extension, basal ganglia circuit dynamics [17]. Together, the PT320 and exendin-4 studies provide rare and important evidence that GLP-1 pathway activation exerts not only structural neuroprotection but also functional circuit-level rescue.

Liraglutide, semaglutide, and lixisenatide have not yet been dissected at this same electrophysiological resolution, but structural and behavioral data suggest similar synaptic preservation. In chronic MPTP and 6-OHDA models, liraglutide and semaglutide preserve tyrosine hydroxylase-positive cell bodies, protect axonal projections and synaptic markers such as dopamine transporter, vesicular monoamine transporter, and synaptophysin, and ameliorate motor deficits [6,18,27]. Lixisenatide, in both MPTP and PFF models, protects dopaminergic neurons and improves motor performance in parallel with its effects on α-synuclein pathology and mitochondrial function [9]. Engineered GLP-1–secreting bacteria also preserve dopaminergic markers and locomotor behavior in MPTP and A53T models, reflecting sustained circuit function under less direct pharmacologic control [24,25].

Synthesizing these findings, recent reviews propose that GLP-1 pathway activation may help normalize network-level dysfunction in PD, including pathological beta-band oscillations and impaired corticostriatal synaptic plasticity, by preserving dopaminergic drive and by modulating intrinsic excitability and mitochondrial support of synapses [2,4]. While direct documentation of such oscillatory and plastic changes remains limited, the existing synaptic and electrophysiological evidence suggests that GLP-1RAs contribute meaningfully to circuit-level resilience [1].

GLP-1 Pathway Activation, Insulin Signaling, and Metabolic Crosstalk in PD

A defining feature of GLP-1-based therapies is their impact on insulin signaling and systemic metabolism. PD itself is increasingly linked to brain insulin resistance, and a substantial subset of patients has metabolic syndrome or type 2 diabetes. Recent work clarifies how GLP-1 pathway activation influences insulin/IGF pathways in PD-relevant systems.

Direct, detailed neuronal exosome data from exenatide-treated PD patients predate 2021, but multiple recent reviews have revisited this work. They describe that exenatide treatment increased phosphorylation of neuronal insulin receptor and IRS-1 at activating sites, enhanced Akt and mTOR activation, and decreased inhibitory IRS-1 serine phosphorylation in neuron-derived exosomes from PD patients, findings consistent with improved brain insulin signaling. These observations are repeatedly emphasized in contemporary syntheses as proof-of-concept that GLP-1RAs can reverse neuronal insulin resistance in human PD [1,19,23].

In the post-2021 primary literature, semaglutide and liraglutide demonstrate similar effects in cellular and animal models. In one of the researches it was shown that in 6-OHDA-treated SH-SY5Y cells, semaglutide and liraglutide activated IRS-1/Akt/CREB signaling and that this activation coincided with reduced oxidative stress, enhanced autophagy, decreased α-synuclein accumulation, and improved survival [6]. 2023 LUHMES study likewise found that liraglutide and dual incretin agonists restored Akt signaling and survival pathways under chronic ER stress while normalizing ER–mitochondrial crosstalk and autophagy [3]. These data demonstrate that GLP-1R-mediated re-sensitization of insulin/IGF pathways is mechanistically upstream of multiple protective processes.

The importance of metabolic crosstalk is underscored by PD–diabetes comorbidity models. In a streptozotocin plus MPTP model, liraglutide was found to improve body weight and glycemic control, reduce necroptosis-related proteins, and suppress NF-κB signaling in the brain, leading to enhanced motor performance and preservation of dopaminergic neurons. These findings suggest that improved systemic insulin sensitivity and attenuated inflammation contribute

directly to central neuroprotection. [20]. In a high-fat diet plus streptozotocin and rotenone rat model, semaglutide, administered with or without metformin, significantly normalized blood glucose, HOMA-IR, HbA1c, and lipid parameters. Treatment also enhanced brain antioxidant status, reduced oxidative–inflammatory biomarkers, and improved locomotor, cognitive, and olfactory functions. [18]. These findings indicate that GLP-1RAs can coordinate improvements in peripheral and central insulin metabolism, thereby targeting a major component of PD pathophysiology.

Dual GLP-1/GIP agonists further emphasize the centrality of insulin/IGF signaling. In vitro and in vivo work with DA-CH5 and DA5-CH shows that dual agonists more strongly activate IRS-1/Akt/CREB signaling, enhance mitochondrial biogenesis and autophagy, reduce inflammation, and lower α-synuclein levels than single GLP-1RAs in PD models [8,15,29]. In a rotenone rat model, tirzepatide produced greater improvements in motor function, striatal dopamine levels, and reductions in inflammatory markers and α-synuclein accumulation compared with exendin-4 [26]. Reviews emphasize that these dual agonists might represent a next generation of incretin-based neuroprotective agents with enhanced central insulin pathway engagement [2,4].

Collectively, this body of work supports viewing GLP-1 pathway activation as a strategy to correct brain insulin resistance and its systemic correlates in PD, thereby indirectly improving mitochondrial function, proteostasis, and synaptic resilience [6,18].

Comparative Mechanistic Profiles of GLP-1-Based Interventions

Although all GLP-1-based interventions share core mechanisms, recent studies and reviews allow a preliminary differentiation of mechanistic niches.

Exendin-4, delivered either as conventional exenatide or sustained-release PT320, is particularly well characterized for its effects on microglial activation and neuroinflammation, as well as for its electrophysiological and synaptic impact. Work since 2021 has reinforced exendin-4's ability to attenuate microglial and astrocytic activation, shift microglia toward anti-inflammatory phenotypes, and suppress inflammasome signaling, while PT320's MitoPark studies and Liu's electrophysiology data show that exendin-4 preserves synaptic dopamine release and nigral firing in vivo [16,17,29]. Earlier human exosome data, now repeatedly summarized in recent reviews, suggest that exenatide also restores neuronal insulin signaling in PD patients [2,19,23].

Liraglutide has the most detailed mitochondrial and inflammatory mechanistic work in PD models. It clearly enhances PINK1/Parkin-dependent mitophagy, regulates PGC-1α-driven mitochondrial biogenesis and fission–fusion balance, and suppresses AMPK/NF-κB-mediated neuroinflammation and necroptosis, especially in PD–diabetes contexts [5,13,14]. It also improves ER stress responses and autophagy in human dopaminergic-like neurons [3,28]. These data position liraglutide as a prototypical agent for targeting mitochondrial/ER stress and inflammation in PD, especially in metabolically compromised patients.

Semaglutide stands out for its coherent autophagy α-synuclein package and its combined central–peripheral metabolic effects. In 6-OHDA models, semaglutide enhances autophagic flux, improves lysosomal function, reduces α-synuclein accumulation, and protects dopaminergic neurons, while also reducing oxidative stress and restoring IRS-1/Akt/CREB signaling [6,27]. In diabetic plus rotenone models, it simultaneously improves systemic metabolic parameters and brain oxidative–inflammatory status [18]. This profile makes semaglutide an attractive candidate for α-syn-centric and metabolic comorbidity-focused strategies.

Lixisenatide, though studied in fewer PD models, brings a unique mechanistic focus: it has been shown to reduce α-synuclein phosphorylation, aggregation, and, crucially, PFF-driven

propagation, while mitigating mitochondrial dysfunction and apoptosis and protecting dopaminergic neurons and motor function [18]. This positions lixisenatide as an interesting candidate for intervening early in the course of PD, when blocking α-synuclein propagation may have the greatest impact.

Dual GLP-1/GIP agonists, including experimental molecules such as DA-CH5 and DA5-CH and the clinically approved tirzepatide, appear to enhance many of the same mechanisms more robustly. They often show superior activation of IRS-1/Akt/CREB signaling, stronger effects on mitogenesis and autophagy, greater suppression of NF-κB and pro-inflammatory cytokines, and more pronounced reductions in α-synuclein load and dopaminergic loss than single GLP-1RAs [8,26,29]. Recent reviews suggest that such dual agonists may represent a rational evolution of GLP-1-based neuroprotective therapeutics [2,4].

Engineered GLP-1–secreting bacteria such as L. lactis MG1363-pMG36e-GLP-1 and E. coli Nissle 1917-GLP-1 occupy a different but related niche, demonstrating that continuous gut-derived GLP-1 signaling can modulate microglial states, ferroptosis, and gut–brain inflammation, reduce α-synuclein pathology, and protect dopaminergic neurons [11,24,25]. Though not ready for clinical translation, these approaches highlight the importance of gut–brain interactions and suggest future possibilities for microbiome-mediated GLP-1 pathway modulation.

Clinical Evidence and Translational Trajectory

Most of the detailed mechanistic evidence reviewed here is preclinical; however, clinical and meta-analytic data published since 2021 continue to support these findings and encourage further translational development. A focused review of exendin-4 in Parkinson's disease summarized both preclinical and early clinical evidence for motor improvements, potential disease-modifying effects, and mechanistic plausibility based on exendin-4's actions on mitochondrial function, inflammation, and insulin signaling. [23]. Recent evaluations have revisited exendin-4's potential as a therapeutic for Parkinson's disease, emphasizing that its diverse mechanistic targets including mitochondrial support, anti-inflammatory actions, and modulation of insulin signaling make it a promising candidate for further clinical investigation [19,22].

Broader reviews published in 2022 and 2024 expanded the scope to encompass other GLP-1RAs and dual agonists. Reich and Hölscher in 2022 synthesized evidence across Alzheimer's disease and PD, emphasizing GLP-1-induced improvements in synaptic protection, amyloid and α-synuclein pathology, mitochondrial function, and insulin signaling [1]. In 2022 it was reviewed that GLP-1 and GIP receptor agonists in PD, summarizing preclinical and clinical data, highlighting dual agonists such as DA-CH5 and DA5-CH, and outlining mechanistic pathways to be captured in future trials [2]. In 2024 focusing specifically on GLP-1 class drugs in PD, emphasizing dopaminergic protection, energy metabolism normalization, and anti-inflammatory and proteostatic effects, and arguing for their further development as disease-modifying agents [4].

Most recently, in 2025, a systematic review and meta-analysis of randomized controlled trials evaluated the efficacy of GLP-1 receptor agonists in Parkinson's disease, including exenatide, liraglutide, and lixisenatide. They concluded that GLP-1RAs yield statistically significant improvements in motor scores (MDS-UPDRS) compared with placebo or standard of care, with acceptable safety profiles. At the same time, they emphasized that existing trials are relatively small, often short in duration, and frequently lack systematic mechanistic biomarker programs, making it difficult to prove disease modification or directly link clinical outcomes to specific pathways. They recommended larger, longer, biomarker-rich phase II–III trials to determine

whether the mechanistic potential demonstrated preclinically translates into slowed dopaminergic degeneration and clinical progression [12].

These clinical syntheses collectively confirm the translational promise of GLP-1RAs and dual agonists in PD and align with the mechanistic narrative outlined above. They provide a strong rationale for designing future trials in which clinical endpoints are complemented by imaging and fluid biomarkers capturing mitochondrial function, neuroinflammation, α-synuclein proteostasis, and insulin signaling [12,19].

Toward Mechanism-Anchored Disease-Modifying Strategies

The multi-axis mechanistic picture emerging from post-2021 studies suggests several principles for designing future disease-modifying strategies based on GLP-1 pathway activation.

First, drug selection can be aligned to dominant mechanistic hypotheses or patient subgroups. Liraglutide may be particularly suitable for PD patients with prominent mitochondrial/ER stress and metabolic co-morbidities, semaglutide for those in whom α-synuclein pathology and autophagic failure are central, lixisenatide for early or prodromal PD where blocking α-synuclein propagation is critical, and exendin-4-based formulations for scenarios in which circuit-level dopaminergic firing and microglial modulation are key. Dual GLP-1/GIP agonists might be preferred where strong engagement of insulin/IGF signaling and broad mitochondrial, inflammatory, and proteostatic benefits are desired [5,6,9].

Second, trials should incorporate mechanistic biomarkers aligned with the axes discussed. Possible measures include neuronal exosome assays of insulin receptor/IRS-1/Akt/mTOR and autophagy signaling; cerebrospinal fluid markers of α-synuclein species, neurofilament light chain, inflammatory cytokines, and oxidative stress; dopaminergic PET for terminal integrity; FDG-PET or MR spectroscopy for brain metabolic status; and plasma markers of insulin sensitivity and low-grade inflammation. Such biomarkers would help demonstrate target engagement, validate mechanistic hypotheses in humans, and support claims of disease modification beyond clinical scores.

Third, early intervention may be essential. Because some GLP-1RAs, such as lixisenatide, appear able to limit α-synuclein propagation, and others maintain mitochondrial and synaptic function, deploying these agents in prodromal PD or very early disease, possibly in genetically or biomarker-defined high-risk populations, might yield greater disease-modifying effects than treating late-stage disease.

Fourth, combination strategies could leverage complementary mechanisms. GLP-1RAs could be combined with metformin, which activates AMPK and modulates mitochondrial function; with anti-α-synuclein immunotherapies or small-molecule aggregation inhibitors; with exercise or lifestyle interventions that enhance mitochondrial biogenesis and neurogenesis; or with microbiome-modulating approaches, including engineered GLP-1–secreting probiotics. Early preclinical evidence, such as semaglutide plus metformin or GLP-1 plus plumbagin combinations, suggests that additive or synergistic neuroprotective effects are possible [18,30].

Finally, careful stratification by metabolic status, genetic factors (e.g., GBA or LRRK2 mutations, α-synuclein gene dosage), and baseline inflammatory or proteostatic signatures will likely be crucial for identifying subgroups that derive the most benefit from GLP-1-based interventions and for interpreting mechanistic biomarker changes in heterogeneous patient populations.

Conclusions

Since 2021, research on GLP-1 pathway activation in Parkinson's disease has significantly expanded, enabling the construction of a coherent mechanistic framework that integrates mitochondrial, inflammatory, proteostatic, synaptic, and metabolic dimensions of neuroprotection. Across diverse preclinical models, GLP-1 receptor agonists and related

incretin-based interventions demonstrate convergent and complementary effects: they enhance mitochondrial quality control by promoting mitophagy, stimulating PGC-1α–dependent biogenesis, and restoring fission–fusion balance, thereby reducing reactive oxygen species, stabilizing mitochondrial membrane potential, and protecting against apoptosis. These mitochondrial benefits are accompanied by potent anti-inflammatory actions, including suppression of microglial and astrocytic activation, inhibition of NF-κB and NLRP3 inflammasome signaling, and interference with regulated cell death pathways such as necroptosis and ferroptosis. GLP-1 pathway activation also supports proteostasis by normalizing autophagic flux, restoring ER–mitochondrial communication, reducing α-synuclein burden, and, in some contexts, limiting prion-like propagation of pathological aggregates. At the functional level, these mechanisms preserve dopaminergic synaptic transmission and substantia nigra pars compacta firing patterns, thereby maintaining basal ganglia network integrity and motor output. Moreover, GLP-1RAs re-sensitize neuronal and systemic insulin/IGF signaling and improve metabolic homeostasis, which may further reinforce central neuroprotection, particularly in models combining PD with diabetes or metabolic stress.

Different GLP-1RAs and related interventions contribute complementary strengths within this overarching framework. Exendin-4 demonstrates broad effects across mitochondrial, inflammatory, and proteostatic pathways; liraglutide has robust mechanistic support for mitophagy and PGC-1α–dependent mitochondrial biogenesis; semaglutide emphasizes antioxidant defense coupled with autophagy-mediated α-synuclein clearance; lixisenatide links mitochondrial protection to attenuation of α-synuclein propagation; dual GLP-1/GIP agonists provide enhanced anti-inflammatory and neurotrophic efficacy; and GLP-1–secreting probiotics illustrate the potential of chronic, gut-mediated modulation of systemic and central inflammation. Clinical and meta-analytic data through 2025 reinforce the safety and symptomatic efficacy of GLP-1RAs in PD, particularly with respect to motor outcomes, yet the critical question of whether these agents can truly alter disease progression remains unanswered. Addressing this will require rigorously designed, biomarker-rich, mechanistically informed trials that directly test the axes of mitochondrial, inflammatory, proteostatic, synaptic, and metabolic modulation elucidated in preclinical studies. If successful, GLP-1-based interventions have the potential to become a central component of future disease-modifying strategies for Parkinson's disease, offering a coordinated, multifaceted approach capable of simultaneously targeting the core pathological processes driving neurodegeneration.

Disclosure

Author's contribution

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All authors have read and agreed with published version of the manuscript.

Funding statement: No applicable.

Institutional review board statement: Not applicable.

Informed consent statement: Not applicable.

Data availability statement: The authors confirm that the data supporting this study are available in the article's references.

Conflict of interest: Authors declare no conflict of interest.

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