Could glucagon like peptide-1 agonists be therapeutic targets in Parkinson's Disease ?

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Abstract

The therapeutic potential of glucagon-like peptide-1 (GLP-1) receptor agonists in Parkinson's Disease (PD) is an area of active investigation, with promising, albeit still preliminary, findings. While not a direct treatment for the underlying neurodegeneration, GLP-1 agonists may offer several beneficial effects relevant to PD pathology and symptoms: Some studies suggest GLP-1 agonists may exert neuroprotective effects by reducing oxidative stress, inflammation, and apoptosis (programmed cell death) in dopaminergic neurons. This is partly attributed to their ability to stimulate neurotrophic factors like brain-derived neurotrophic factor (BDNF). Improved Mitochondrial Function: Mitochondrial dysfunction plays a significant role in PD pathogenesis. GLP-1 agonists have shown to improve mitochondrial function and biogenesis, potentially mitigating the energy deficits seen in PD. Given the growing understanding of the gut-brain axis in PD, the impact of GLP-1 agonists on gut microbiota composition and function is of interest. These agonists may indirectly influence the gut environment, potentially reducing inflammation and improving gut barrier integrity, factors implicated in PD progression. Many individuals with PD experience metabolic complications, including weight loss, insulin resistance, and diabetes. GLP-1 agonists' well-established effects on glucose homeostasis, appetite regulation, and weight management could indirectly improve overall health and quality of life in PD patients. Some studies have reported improvements in motor symptoms in PD patients treated with GLP-1 agonists, although the mechanism behind this is not fully understood and requires further investigation. It could be related to their influence on neurotransmitter systems or improved overall health. However, it's crucial to acknowledge limitations: Current evidence is largely based on preclinical studies and small clinical trials. Larger, well-designed clinical trials are needed to definitively establish the efficacy and safety of GLP-1 agonists as a treatment for PD. The potential mechanisms of action still require further elucidation. Furthermore, the optimal dosage and duration of treatment remain to be determined. In summary, while the evidence is promising, GLP-1 receptor agonists are not yet established as a therapy for PD. Further research is needed to fully assess their therapeutic potential and determine their role within a comprehensive PD management strategy.

Keywords: glucagon like peptide-1, Parkinson's Disease

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Introduction

Among the many neurodegenerative illnesses, Parkinson's disease (PD) ranks high. Between 1% and 2% of those over the age of 65 are affected, and that number increases to 3-5% of those over the age of 85 [1]. There will likely be 12 million new cases of PD, a terrible disease, diagnosed by 2040 due to the disease's steadily rising frequency. Resting tremor, bradykinesia, rigidity, postural instability, and freezing episodes are the motor symptoms most commonly associated with Parkinson's disease (PD). However, a wide range of non-motor features, including cognitive decline, behavioral symptoms, sleep disturbances, exhaustion, autonomic symptoms, and sensory problems, are also common, and are frequently observed as prodromal features of the disease [3,4]. Depletion of dopamine in the striatum due to selective and progressive deterioration of dopaminergic neurons in the substantia nigra is a pathological hallmark of the disease, as is the presence of Lewy bodies in the surviving neurons [1].

Unfortunately, there is currently no way to stop or slow down the progression of neurodegeneration; instead, treatments for Parkinson's disease focus on alleviating symptoms. Since PD is primarily caused by a lack of this neurotransmitter, restoring dopamine levels is the primary goal of contemporary PD treatment. The current gold standard for Parkinson's disease treatment, l-dopa, can lead to motor problems, variations in motor control, and dyskinesias, which can lead to significant disability for many patients over time [4]. These days, researchers are putting a lot of effort into developing alternative therapeutic drugs that target different pathways in the etiology of PD. The gut-brain axis homeostasis is essential for the maintenance of health in both the central nervous system (CNS) and the peripheral system, and these systems can influence one another in multiple pathways. Recent data highlight similarities between neurodegenerative diseases, such as PD and type 2 diabetes mellitus (T2DM) [5]. Although the US Food and Drug Administration (FDA) has granted a license to GLP-1R agonists for the treatment of type 2 diabetes, these drugs are also under intense investigation as potential novel PD-modifying medicines with the potential to influence many pathways of PD pathogenesis. Curiously, antidiabetic medication use, including GLP-1 receptor agonists and dipeptidyl peptidase IV (DPP-IV) inhibitors, was associated with a lower prevalence of PD in type 2 diabetes mellitus (T2DM) patients, which may indicate a neuroprotective impact of these medicines [6,7]. A "stroke protective" effect has also been observed with these medications, suggesting they may play a significant role in neurological diseases [8,9]. Several preliminary investigations have identified these compounds' potential neurotrophic and neuroprotective actions. The processing of amyloid-beta precursor proteins can be altered and protected from oxidative damage by GLP-1 agonists. These peptides also regulate neuronal plasticity and cell survival and exhibit neurotrophic and neuroprotective properties [10,11,12,13]. This review summarizes the most recent findings on the shared pathogenic pathways between type 2 diabetes and Parkinson's disease. It covers: (a) the function of glucagon-like peptide-1 (GLP-1) and GLP-1 receptors, (b) the progress made in creating agonists that target the GLP-1 receptor, and (c) the present state of knowledge about the potential of these new drugs to modify disease, according to data derived from animal models and both preclinical and clinical research. Also covered are the inner workings of GLP-1 receptor agonists, which are potential treatment targets for Parkinson's disease.

2. T2DM and PD: Diseases with Overlapping Pathophysiology?

High blood glucose levels caused by insulin resistance in insulin-sensitive organs such the liver, adipose tissue, and muscles are the hallmarks of type 2 diabetes mellitus [14]. An important aspect of PD pathophysiology is the hypothesis that dysregulated insulin signaling may initiate or hasten the progression of the illness. The vast majority of evidence points to type 2 diabetes as a potential cause of Parkinson's disease. A recent meta-analysis and comprehensive review found that people with type 2 diabetes had a 1.34 times higher chance of developing Parkinson's disease (PD) with more severe motor symptoms [15]. However, earlier research in populations suggested that T2DM may raise the incidence of PD by about 40% [16,17]. Another study found that the risk ratio of PD in type 2 diabetic individuals increased with the length of their diabetes, reaching 1.618 in patients whose diabetes had persisted for more than five years [18]. The AKT insulin signaling pathway is primarily implicated in the association between insulin resistance and dopamine degradation [19]. Several molecules downstream of this pathway, including FoxO, mTOR, and GSK3β, play important roles in the development of Parkinson's disease (PD), including α-synuclein degradation, mitochondrial biogenesis, inflammation, and oxidative stress. Insulin resistance has been linked to increased α-synuclein expression, mitochondrial dysfunction, and oxidative stress in diabetes-induced MitoPark mice, which is an intriguing finding [20]. In addition, insulin resistance, neuroinflammation, and elevated α-synuclein levels were seen in MPTP-PD mice models [21]. Patients with PD who also have dementia are at increased risk for insulin resistance and abnormal glucose metabolism [22,23]. It is worth noting that in a model of Parkinson's disease in rats, the activation of the peroxisome proliferator-activated receptor gamma (PPAR-γ) provided protection against memory impairment caused by MPTP [24]. This receptor enhances insulin sensitivity and glucose metabolism. Insulin administered transdermally ameliorated motor impairments and enhanced mitochondrial function in a recent study using a 6-OHDA PD rat model [25]. Cognitive function and the Unified Parkinson's Disease Rating Scale (UPDRS) score were both shown to improve with intranasal insulin in a small randomized controlled trial [26]. Insulin desensitization, which occurs with prolonged insulin use and reduces insulin's effectiveness, is a known side effect of the drug. To circumvent this, normoglycemic patients may benefit from new alternative treatments that do not worsen insulin desensitization and do not impact blood glucose levels [27]. All of the aforementioned evidence points to the possibility that type 2 diabetes and Parkinson's disease have certain shared pathogenic pathways, which have been the focus of therapeutic efforts in recent years. The FDA-approved GLP-1R agonists have lately shown promise as therapeutic agents in PD, raising hopes for the discovery of new PD medicines with neuroprotective properties or the ability to stop or reverse disease development.

3. GLP-1 and GLP-1 Receptor

After food is consumed, the distal intestine ileum and colon L-cells emit GLP-1, an endogenous 30-amino-acid multifunctional peptide that is formed by proteolytic cleavage of proglucagon molecules. GLP-1 is also made in the central nervous system, specifically in the brainstem's solitary tract neurons. Research has demonstrated that GLP-1 influences a wide range of neural processes, including but not limited to: thermogenesis, energy balance, neurogenesis, blood pressure regulation, and retinal repair. While in the pancreas, GLP-1 improves insulin production and secretion, increases the number and survival of pancreatic β-cells, and decreases both glucagon release and β-pancreatic cell death. In addition to improving adipocyte glucose absorption and

lipolysis, GLP-1 can raise muscular glucose uptake. Reduced hunger, delayed stomach emptying, and reduced gastric acid output are other side effects. It causes mild natriuresis in the kidneys. In addition to its vascular beneficial actions, GLP-1 raises cardiac contractility and heart rate [28,29]. Seven proteins that traverse the cell membrane and are members of the B1G protein-coupled receptor family are known as GLP-1 receptors (GLP1-Rs), and they are the targets of GLP-1's action. The 463-amino-acid GLP1 receptors are expressed in islet cells of the pancreas and other organs including the lungs, heart, kidneys, and brain, where they exert indirect metabolic effects [30]. Hypothalamus, hippocampus, subventricular zone, striatum, substantia nigra, cortex, and brain stem are the brain regions where it is expressed. Specifically, GLP-1R expression has been found in neurons, microglia, and astrocytes in these important brain areas [31]. Cardioprotection, enhanced endothelial function, and reduced inflammation have all been linked to GLP-1. Because they are able to penetrate the blood-brain barrier (BBB) and do not have their half-life cut short by the DPP-IV enzyme, GLP1-Rs are promising new therapeutic options for neurological disorders. In sum, PD may benefit from targeting GLP-1 and GLP1-Rs as a potential treatment target because of the several roles they play in the gut/brain axis.

Agonists for the GLP-1 Receptor

One class of drugs used to treat type 2 diabetes is GLP-1 and GLP1-Rs. But GLP1-Rs have the potential to penetrate the BBB and avoid inactivation by DPP-IV, making them a good choice for treating neurodegenerative illnesses like PD. The duration of action and the amount of injections required categorize GLP-1R agonists as either short-acting or long-acting [19,29]. Injecting long-acting preparations like lixisenatide and liraglutide once daily is the norm, whereas injecting short-acting preparations like exenatide two or three times daily is necessary. Semaglutide, dulaglutide, and a long-acting release version of exenatide are all examples of long-acting preparations that often require weekly injections. The first medication used to treat type 2 diabetes was exenatide. This is a man-made variant of exendin-4, a peptide that binds to GLP-1Rs, shares 53% of its amino acid sequence with native GLP-1, and is resistant to DPP-IV. The half-life of exendin is brief; following a subcutaneous injection of more than 0.2 μg/kg, it is detectable in plasma within 15 minutes and continues for around 15 hours. Another synthetic peptide produced from the exendin-4 hormone, lixisenatide has a half-life of approximately three hours and a binding affinity for the GLP-1R that is four times higher. Its pharmacological impact lasts longer since its rate of dissociation from the receptor is likewise slower. Additionally, a pegylated variant of exendin-4 (NLY-01) with extended half-life has just been created. Liraglutide, a recombinant analogue of GLP-1, binds to albumin, causing its delayed absorption and prolonged plasma half-life of more than 13 hours. There are fewer side effects and better improvements in decreasing glycated hemoglobin and fasting blood glucose with liraglutide compared to short-acting GLP-1R agonists. The recombinant fusion protein albiglutide has a half-life of five days and binds to albumin. It is composed of two copies of a 30-amino acid sequence of modified human GLP-1. A human Ig G4-fragment crystallizable (Fc) heavy chain, created by recombinant DNA technology, is covalently bonded to two GLP analogs protected by DPP-IV to form dulaglutide. Subcutaneous injection often reaches its peak 48 hours after administration, and its half-life is quite lengthy. Another GLP-1 analog, semaglutide, has decreased DPP-IV sensitivity as well. Indeed, it is a liraglutide variant that has significantly improved blood plasma half-life. Notably, agonists that maximize the therapeutic effects and minimize the detrimental effects of these medications have been developed, including dual and triple GLP-1R/Gastric inhibitory polypeptide receptor (GIP-R) agonists. Tirzepatide has

a longer half-life of 5 days compared to other combination GLP-1R/GIP-R agonists because of its high albumin affinity. It is structurally a 39-amino-acid peptide that contains the bioactive sequence of gastric inhibitory polypeptide (GIP) and a sequence that acts on GLP-1 by substituting its intermediate amino acid; additional agents include DA-JC1, DA2, DA-CH3, DA-JC4, and DA-CH5. Interestingly, the Food and Drug Administration has authorized the use of monomeric GLP-1R agonists (e.g., semaglutide and liraglutide) and dual GLP-1R agonists (e.g., tirzepatide) for the treatment of type 2 diabetes and metabolic disorders, including the management of chronic weight in individuals who are obese [32,33]. Neuroprotective benefits have also been shown with triagonist, a synthetic monomeric peptide receptor agonist that includes GLP-1, GIP, and glucagon activities [19]. Typically, the extent to which these medications can penetrate the brain is proportional to how well they protect the brain. Recent research on incretin receptor agonists found that liraglutide, semaglutide, and Peptide 18 were unable to pass the blood-brain barrier (BBB), in contrast to exendin-4, lixisenatide, Peptide 17, DA3-CH, and DA-JC4. Importantly, exendin-4 and DA-JC4 have the strongest ability to traverse the BBB [34], making them potential therapeutic agents for neurodegenerative illnesses like PD among the non-acylated, non-PEGylated incretin receptor agonists studied. Additionally, a new study demonstrated that GLP-1R agonists can pass the blood-brain barrier (BBB) both quickly and slowly. Actually, the rate of brain uptake was lowest for tirzepatide and highest for albiglutide and dulaglutide, with DA5-CH following closely after [35]. Notably, GLP1-Rs are a novel class of compounds that, according to recent data from animal models, preclinical research, and clinical trials, may pave the way for novel approaches to treating PD.

5. GLP-1 Receptor Agonists in Parkinson's Disease Treatment

Potential new treatment drugs for Parkinson's disease have been the focus of extensive study into GLP1-R agonists. Restoring dopamine levels, inhibiting dopaminergic loss, attenuating neuronal degeneration, and alleviating motor and non-motor aspects of PD can be achieved with GLP1-R agonists, according to animal models of PD and preclinical investigations. Clinical trial results are also quite encouraging, raising the prospect of GLP1-R agonists being added to the existing toolbox of medications for PD treatment.

5.1. Evidence from Animal Models: Preclinical Studies

Exendin-4 and other novel incretin analogs were discovered to increase the survival rate of dopaminergic SH-SY5Y neuroblastoma cells by improving autophagy and protecting them from mitochondrial stress caused by the hazardous mitochondrial complex I inhibitor rotenone [36]. Neurones expressing tyrosine hydroxylase (TH) were more highly expressed after peripheral injection of GLP-1R agonists [37]. The TH enzyme is essential for the production of dopamine [38]. Additionally, exenatide increased dopamine levels and improved motor skills in diabetic rats with MPTP-induced PD [39,40,41,42], while protecting dopaminergic neurons against 6-OHDA and MPTP toxicity. In addition, the death of hippocampus neurons caused by injection of toxin lipopolysaccharide was reduced in mice when exendin-4 was administered continuously, and it had a protective impact on cognitive-related neurotransmission systems [43]. Exendin-4 improved motor symptoms, improved monoaminergic neurotransmission by affecting the expression of vesicular monoamine transporter 2, and alleviated TH-positive neuronal loss and terminal denervation in a rat model of α-synucleinopathy associated with Parkinson's disease [44].

Exenatide, in its modified form NLY01, prevented the death of dopaminergic neurons in a different animal paradigm by blocking the microglial-mediated neurotoxic phenotypic transition in astrocytes [45]. Another mechanism by which GLP-1 receptor agonists reduce inflammation is by blocking the effects of Toll-like receptor agonists [46]. Curiously, when it came to PD pathology, the dual agonist DA5-CH was determined to be more efficacious than NLY01 in a study using an MPTP mouse model [47]. Dopaminergic neurons were discovered to be sustained in rats following 6-OHDA lesioning by a sustained-release exenatide drug called PT302 [48]. Treatment with PT320 early on improved L-DOPA-induced dyskinesia in a PD mouse model, suggesting that it may be able to reduce the severity of dopaminergic degeneration, according to a recent study [49]. Replicating these findings is necessary [51], but it is worth mentioning that lixisenatide and liraglutide were discovered to be more efficient than exenatide in protecting against MPTP-induced dopaminergic degeneration [50]. Both exendin-4 and linagliptin restored motor performance, glial activation, and dopaminergic neuronal death in a recent MPTP PD mouse research [52]. Semaglutide, when given once weekly, restored TH levels in MPTP-treated mice more effectively than liraglutide, when given once daily [53,54]. In a mouse model of MPTP PD, a new GLP-1 analog called Val(8)GLP-1-GluPal showed neuroprotective benefits, and its serum half-life was longer than exendin-4's [55]. On top of that, sitagliptin and liraglutide enhanced motor performance and stopped the inflammatory-apoptotic degenerative process in a rotenone-induced nigral neuronal loss model of Parkinson's disease [56,57].

In the realm of dual GLP-1/GIP receptor agonists, DA-JC1 has shown promising results in both animal models (MPTP mice) and in vitro studies (SH-SY5Y cells exposed to ROT-induced mitochondrial stress) [35], outperforming previous GLP-1 analogs [61]. When it came to restoring TH levels, DA3-CH outperformed liraglutide in a separate MPTP mice research [62]. A recent study found that when it came to protecting dopaminergic neurons, suppressing inflammation, and increasing TH expression in the substantia nigra, DA5-CH outperformed semaglutide. Both medications decreased α-synuclein aggregation and insulin resistance, whereas DA5-CH showed superior results [63]. The motor symptoms of PD could be alleviated in rats with ROT lesions by administering a combined GLP-1R/GIPR agonist [64]. When comparing liraglutide to DA-JC4, DA-CH5, and DA-JC1 at the same dosage in an MPTP PD mouse model research, DA-JC4 and DA-CH5 proved to be the most efficacious [65,66]. In addition, DA-CH5 was discovered to be more effective than NLY01 in reducing inflammation and neurodegeneration [47,67].

5.2. Evidence from Clinical Studies

The effects of GLP1R agonists on PD pathophysiology have been the subject of several previous clinical investigations, with encouraging preliminary findings.

Table 1. Results of GLP-1Rs agonist clinical trials in PD patients.

ClinicalTrial.Gov Identifier	Drug	Result	Reference
NCT01174810	Exendin-4	Improvement in MDS-UPDRS and Mattis DRS-2	[68]
NCT01971242	Exendin-4	Improvement in MDS-UPDRS	[69]
NCT02953665	Liraglutide	Improvement in daily living of PD patients	[70]
NCT03439943	Lixisenatide	Improvement in MDS-UPDRS III	[71]

Exendin-4 was given twice daily to 45 PD patients with intermediate disease for one year in a randomized, single-blind, open-label trial (NCT01174810) [68]. Traditional PD therapy was administered to the patients. Patients with PD who did not get this medication served as a control group. A 2-month wash-out interval was imposed in this investigation. Motor function as judged by the Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS) and cognitive function as determined by the Mattis dementia rating scale-2 (Mattis DRS-2) showed a significant difference after 14 months. After a 12-week wash-out period, these positive effects persisted in the follow-up evaluation [72]. When it came to subjective assessments of quality of life and depression, nothing changed. During the same time span, the untreated control group showed a rapid decline, demonstrating that exendin-4 had the ability to change the disease. One person was unable to finish the trial due to weight loss, which was a major worry among the adverse events mentioned by trial participants; nevertheless, this impact was completely reversed following drug withdrawal. Exenatide was also associated with gastrointestinal issues, the most prevalent of which were nausea and constipation. It was determined that none of the major side effects reported were responses to exenatide. Constipation, longer periods "off-medication," and weight gain were the most often reported adverse effects in the group taking traditional PD treatment. Curiously, five individuals had to reduce their l-dopa dosages because the exenatide-treated group had a higher increase in the mean dyskinesia rating scale score.

These encouraging findings prompted the same research team to perform a phase II clinical trial (NCT01971242) [69] with 60 PD patients exhibiting moderate illness and using subcutaneous injections of exendin-4 once weekly for 48 weeks. Traditional PD therapy was administered to the patients. A 12-week wash-out period was imposed on this research. Motor control was improved in the exendin-4 group compared to the placebo group following 48 weeks of pharmacological treatment for PD, and this improvement persisted after 60 weeks. This long-lasting positive effect of exenatide may indicate that this medication may affect disease severity for a longer period of time than traditional PD medications. There was no statistically significant difference in the occurrence of side effects, including gastrointestinal problems, across the groups that were evaluated. No major adverse events were determined to be associated with the study interventions out of eight that were recorded, six in the exenatide group and two in the placebo group. Two patients in the placebo group stopped participating because their anxiety and dyskinesia got worse, whereas one patient in the exenatide group stopped because they had asymptomatic hyperamylasemia at 12 weeks. And just after the trial's monitoring period ended, pancreatic cancer struck one patient in the placebo group. While PD patients using exenatide had superior scores on

motor signs, a post hoc study revealed that non-motor indicators, including "emotional well-being" and mood/apathy ratings, did not remain improved after treatment stopped [73]. Exenatide may have superior cognitive effects in obese PD patients with insulin resistance compared to other subgroups of PD, according to a separate post hoc analysis [74]. It is worth mentioning that in this phase II trial, patients with PD who were treated with exenatide had higher levels of phosphorylated mTOR and phosphoinositide-3-kinase/Akt (PI3K/AKT) expression in neuronal-derived exosomes compared to the placebo group [75].

Regarding the effects of liraglutide in PD patients, a phase II clinical trial that was randomized and double-blind was also carried out (NCT02953665). Subjects in this trial ranged from 18 on a placebo to 37 who received an active drug. Conventional PD treatment individuals with PD were given liraglutide subcutaneous injections for 52 weeks. Liraglutide significantly improved the quality of life for PD patients in this trial [70]. Common side effects were responses at the injection site and gastrointestinal issues. The research intervention was unrelated to any of the eleven major side events that were recorded. The analysis of more parameters is ongoing.

Lisisenatide was given orally once daily for one year to individuals with early PD in another randomized, double-blind, placebo-controlled study (NCT03439943). Patients were checked during both the on and off periods. The Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) demonstrated less disability in lixisenatide-treated PD patients, with the most noticeable improvement shown in ON and OFF times [71]. Among those using lixisenatide, nausea was a prevalent adverse effect.

Additionally, there are several current clinical trials that are still awaiting findings that investigate the effects of PT320 (NCT04269642), NLY01 (NCT04154072), semaglutide (NCT03659682), and exendin-4 (NCT04232969, NCT03456687, NCT04305002) on PD patients.

Table 2. Ongoing GLP-1R agonist clinical trials in PD patients.

Title	ClinicalTrials.gov ID	Phase	Status	Intervention	Results Overview
Exenatide Once Weekly Over 2 Years as a Potential Disease Modifying Treatment for Parkinson's Disease (Exenatide-PD3)	NCT04232969	Phase 3	Active, not recruiting	Drug: Exenatide extended release 2 mg (Bydureon)	Result not yet available
Effects of Exenatide on Motor Function and the Brain	NCT03456687	Phase 1	Completed	Drug: Exenatide	No result available
Exenatide Treatment in Parkinson's Disease	NCT04305002	Phase 2	Active, not recruiting	Drug: Exenatide Other: Placebo	No result available
SR-Exenatide (PT320) to Evaluate Efficacy and Safety in Patients With Early Parkinson's Disease	NCT04269642	Phase 2	Active, not recruiting	Drug: PT320 2.0 mg Placebo Drug: PT320 2.0 mg Drug: PT320 2.5 mg	Unknown status
GLP1R in Parkinson's Disease (GIPD)	NCT03659682	Phase 2	Not yet recruiting	Drug: Semaglutide	No result available
A Clinical Study of NLY01 in Patient's With Early Parkinson's Disease	NCT04154072	Phase 2	Active, not recruiting	Drug: NLY01 Drug: Vehicle	No result available

Curiously, GLP-1R agonist responses vary between PD models and patient groups, according to recent research. How well GLP-1R agonists work depends on a number of variables, including genetic abnormalities, disease stage, and PD comorbidities. The incidence of side effects during therapy with GLP-1R agonists may potentially be influenced by these characteristics. The early

prediction of treatment response and the appropriate selection of patients would be greatly assisted by a tailored treatment approach, which would optimize therapeutic efficacy and safety. It is believed that tailored treatment will be made possible by systematic research that address these interindividual variances in treatment response.

5.3. Mechanism of Action

The origins of PD, a diverse neurodegenerative disease, are intricate. Protein misfolding and aggregation, ubiquitin-proteasome system deficiencies and aggregation, inflammation, impaired oxidative stress, and mitochondrial dysfunction are some of the processes that have been linked to PD pathogenesis. The available data suggests that GLP-1Rs influence many pathways (Figure 1).

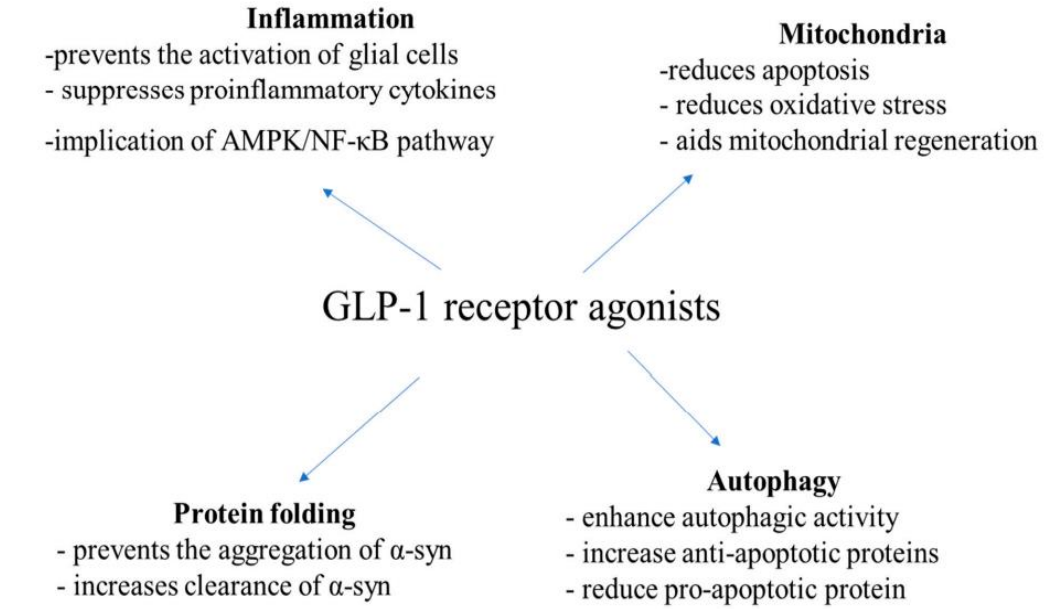

Figure 1. Mechanisms of action of GLP1 receptor agonists according to in vitro and in vivo PD studies.

Exendin-4 limited neuroinflammation and neurodegeneration by preventing glial cell activation, according to in vitro and in vivo investigations [52,76,77,78]. Furthermore, in models where LPS-induced lesions were present, GLP-1 exhibited anti-inflammatory properties [76,79]. In addition, exenatide-4 reduced levels of TNF-α and IL-1β in a dose-dependent manner in a Parkinsonian rat model of α-synucleinopathy [80], lesions produced by 6-OHDA [61] and ROT [41] were also ameliorated. Exendin-4 has been shown in earlier research to reduce levels of inflammatory mediators including IL-6, NF-kB, and cyclooxygenase1 (COX1) [42,80]. It has also been noted that ligandulite and sitagliptin reduce inflammation and microglial activation in rats that have been treated with ROH [56,57]. It has been proposed that liraglutide's neuroprotective effects against inflammation in a mouse model of PD called MPTP could be achieved through the AMP-activated protein kinase (AMPK)/NF-κB pathway [81]. Microglia activation and levels of pro-inflammatory cytokines have also been demonstrated to be affected by novel GLP-1/GIP receptor dual agonists [66,67].

In addition to inflammation, GLP-1Rs have been discovered to influence mitochondrial homeostasis and oxidative stress. Rodents treated with 6-OHDA and ROT-induced lesions showed that GLP-1R prevented cell death by increasing B-cell lymphoma-2 (Bcl-2) and complex

I expression while decreasing caspase-3 expression [82,83]. Exendin-4 and DA-CH5 also decreased ROS levels in 6-OHDA-treated SH-SY5Y cells [61]. By activating nuclear factor erythroid 2-related factor 2 (Nrf-2), as well as the cyclic AMP, PI3K, and protein kinase C pathways, GLP-1 may reduce oxidative stress [84]. In addition, liraglutide has been found to augment mitochondrial regeneration by raising levels of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) and NRF2 expression in mice treated with MPTP [85].

Regarding the role of GLP-1RA in protein folding, liraglutide has been demonstrated to reduce α-syn aggregation in mice induced by MPTP [86]. It is likely that exendin-4 suppresses the PI3K/Akt/mTOR signaling pathway, as it was also linked to enhanced autophagic clearance of overall α-syn and pathogenic pSer129-α-syn in the substantia nigra pars compacta of rats [44]. There is evidence that NLY01 can influence α-syn aggregation in dopamine neurons as well [45].

The expression of sequestosome-1 and Beclin-1 is increased by DA-CH5 and exendin-4, which impacts autophagy as well [61]. In addition to inhibiting caspase-3 action and lowering levels of the pro-apoptotic protein Bax, exendin-4 has been found to raise levels of the anti-apoptotic proteins phospho-Bcl-2 (Ser70) and phospho-BAD (Ser112) [35,87]. It has been proposed that DA-CH5 and exendin-4 exercise their neuroprotective effects in rat 6-OHDA models by promoting autophagy and preventing apoptosis, namely through increasing autophagic activity and decreasing the Bax/Bcl-2 and active caspase-3/caspase-3 ratios [35]. Activation of the PI3K/Akt signaling pathway and downregulation of apoptotic mechanisms, such as poly (adenosine diphosphate (ADP) ribose) polymerase (PARP), have also been noted [88]. In SH-SY5Y cells with ROT-induced mitochondrial damage, GLP-1 mimetics enhance autophagy by upregulating the expression of autophagy-related 3, autophagy-related 7, and LC3A/B [89]. In rats transgenic for AAV-A53T-α, exendin-4 improved autophagy by upregulating mTOR and Akt and boosting LC3-II expression [43]. The amounts of fission and fusion mitochondrial proteins were changed by liraglutide, which restored mitochondrial shape in a mouse model of MPTP [85,86]. Semaglutide was shown to be more effective than liraglutide in protecting SH-SY5Y cells against 6-OHDA cytotoxicity, which was caused by an increase in autophagy flux and a decrease in oxidative stress and mitochondrial dysfunction, according to a recent study [90].

6. Research Gaps and Future Directions

According to recent findings, the neuroprotective efficacy of GLP-1R agonists is directly related to their capacity to penetrate the blood-brain barrier. diverse types of drugs and even compounds within the same class have very diverse pharmacodynamic and pharmacokinetic properties, which are directly related to how well they work. There is a dearth of comprehensive research that would address the fact that some patients may not react as anticipated to GLP-1R agonists in clinical practice. Due to the high levels of study heterogeneity or the short sample size, the best possible interpretation of the results may be compromised. To better understand the effectiveness, ideal dosage, and long-term safety profiles of several GLP-1 analogs in PD, larger clinical trials are required. When confirmed in future clinical trials, genotyping for GLP1R polymorphisms has the potential to aid in the early prediction of treatment response and the selection of individuals that would benefit most from and be least risked by therapy with GLP-1R agonists. Additionally, the exact pathways via which these medicines achieve their neuroprotective benefits should be investigated in more depth in subsequent studies. Improving treatment results for PD will need

the identification of critical routes to target. To reach more definitive conclusions, it is also necessary to conduct large-scale clinical trials in a variety of PD populations to evaluate long-term outcomes. In order to ensure that any variations in clinical outcome measures between treatment groups are actually evidence of disease change and not just symptomatic effects, it is crucial to include a washout period in clinical trial design or conduct long-term follow-up. There would be more proof of illness change if many biomarkers were evaluated. To further investigate the impact of drugs on motor and non-motor symptoms, further randomized controlled trials are required. We eagerly await personalized therapy options that are based on precise genotyping and phenotyping data in order to maximize therapeutic advantages. With the use of AI, PD patients' symptoms can be closely monitored, and personalized treatment plans can be developed. There is hope for better treatment results in PD thanks to precision medicine approaches and the investigation of combo treatments. Additionally, it is important to investigate potential new dual GLP-1/GIP receptor agonists with increased BBB crossing capabilities. Another promising avenue is the enhancement of medication distribution across the blood-brain barrier. There will likely also be an investigation into more user-friendly administration methods, such as oral forms. Future research plans should also assess the potential for interactions between GLP-1R agonists and other traditional dopaminergic medications. Equally important would be learning how these medications may affect different forms of neurodegeneration. It is intriguing to note that PD seems to involve multiple organs, with a complicated relationship between the central and peripheral nervous systems. More study is required to determine if insulin resistance causes or contributes to neurodegeneration in PD, but it is clear that the gut-brain axis is very important. More research on this topic might help in the detection of high-risk individuals, such as those with metabolic syndrome, which could lead to more personalized treatment plans. Potentially more effective treatments for PD and other neurodegenerative diseases may be available in the future if scientists work on nonpeptidergic ligands that alter GLP-1R activity. This would allow GLP-1R agonists to exert their full potential on multiple levels.

7. **Conclusions**

As far as neurodegenerative diseases go, PD is in the top two. Primarily, dopamine replacement treatment is used to alleviate symptoms. Notably, new evidence suggests that insulin resistance contributes to dopamine degradation, dysregulated insulin signaling may be linked to PD, and altered glucose metabolism is observed in several brain areas of PD patients. This data supports the idea that type 2 diabetes is a risk factor for Parkinson's disease. An intriguing development in the therapy of PD is the emergence of GLP-1R agonists, which have recently gained FDA approval for the treatment of type 2 diabetes. In a nutshell, GLP1-R agonists can treat motor and non-motor symptoms of Parkinson's disease (PD), restore dopamine levels, decrease dopaminergic loss, and reduce neuronal degeneration, according to much of data from animal models and preclinical investigations. Improving motor and cognitive skills and daily living parameters of PD patients has been shown in clinical research regarding the effect of GLP1-R agonists such lixisenatide, liraglutide, and exendin-4. This supports the desire to uncover novel PD modifying medications. Some research suggests that GLP1-R agonists may influence processes involved in the development of Parkinson's disease, such as neuroinflammation, oxidative stress, mitochondrial homeostasis, protein folding, autophagy, and apoptosis. We are also eagerly awaiting the findings of many therapeutic trials that try to prevent or even reverse the progression of this terrible disease. The goal is daunting, but not impossible, to accomplish.

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