Review

GLP-1 Receptor Agonists: A New Challenge in Parkinson's Disease Treatment

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Review

GLP-1 Receptor Agonists: A New Challenge in Parkinson's Disease Treatment

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Abstract: Parkinson's disease (PD) is one of the most common neurodegenerative diseases. Recent data highlight similarities between neurodegenerative diseases including PD and type 2 diabetes mellitus (T2DM) suggesting a crucial interplay between the gut–brain axis. Glucagon-like peptide-1 receptor (GLP-1R) agonists, known for their use in T2DM treatment, are currently extensively studied as novel PD modifying agents. For this narrative review article, we searched PubMed and Scopus databases for peer-reviewed research, review articles and clinical trials regarding GLP-1R agonists and PD, published in the English language with no time restrictions. We also screened the references of the selected articles for possible additional articles in order to include most of the key recent evidence. Our research was conducted between February 2023 and February 2024. We used the terms "Glucagon-like peptide-1", "GLP-1 receptor", "GLP-1R agonists", "PD", "T2DM", "insulin", "neurodegenerative disease", "glucose", "animal models", "clinical trials" in different combinations. Many data on animal models and preclinical studies show that GLP1-R agonists can restore dopamine levels, inhibit dopaminergic loss, attenuate neuronal degeneration and alleviate motor and non-motor features of PD. Evidence from clinical studies are also very promising enhancing the possibility of adding GLP1-R agonists in the current armamentarium of drugs available for PD treatment.

Keywords: Parkinson's disease; type 2 diabetes mellitus; GLP1-R agonists; GLP-1; exendin-4; liraglutide; lixisenatide; semaglutide; clinical trials; neurodegeneration

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases. It affects 1-2% of the population above 65 years and this percentage rises to 3-5% at ages beyond 85 years [1]. PD prevalence is continually increasing and by 2040, about 12 million people are expected to be diagnosed with this devastating disease. PD is mainly characterized by motor symptoms such as resting tremor, bradykinesia, rigidity, postural instability and freezing episodes, however a variety of nonmotor features, such as cognitive decline, behavioral symptoms, sleep disturbances, fatigue, autonomic symptoms and sensory problems are described in PD symptomatology [2], often as prodromal characteristics of the disease [3,4]. The pathological hallmarks of the disease are the progressive and selective degeneration of the dopaminergic neurons in the substantia nigra, resulting to dopamine depletion in the striatum, and the presence of Lewy bodies in the remaining neurons [1].

Currently PD treatment aims to the symptomatic relief of PD patients, without being able to prevent or inhibit the process of neurodegeneration. The main target of current PD treatment is the restoration of dopamine levels, as the deficiency of this neurotransmitter is the main cause of PD. However, chronic use of l-dopa which is the gold standard for current PD treatment is frequently associated with the development of motor complications, motor fluctuations and dyskinesias, which in the long run cause severe disability in a large percentage of PD patients [4]. Alternative treatment

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agents are nowadays under intense research targeting different pathways in PD pathogenesis. Recent data highlight similarities between neurodegenerative diseases including PD and type 2 diabetes mellitus (T2DM) [5], suggesting that the homeostasis in the gut–brain axis is fundamental for the maintenance of health in both the central nervous system (CNS) and the peripheral system, and these systems can affect one another in multiple pathways. GLP-1R agonists is licensed by the US Food and Drug Administration (FDA) for the treatment of T2DM, however these agents are currently extensively studied as novel PD modifying agents that can have an impact on multiple mechanisms of PD pathology. This review analyses current data on the common pathogenic pathways between T2DM and PD, describe the role of glucagon-like peptide-1 (GLP-1) and GLP-1 receptors, the development of GLP-1 receptor agonists and the current data regarding the role of these new drugs as disease-modifying agents based on data from studies on animal models, preclinical as well as clinical studies. The mechanisms that GLP-1 receptors agonists could possibly affect as new PD therapeutic agents, are also discussed.

2. T2DM and PD: Diseases with Overlapping Pathophysiology?

T2DM is a disease characterized by high blood glucose levels due deficient insulin secretion and insulin resistance of insulin-sensitive tissues such as the liver, adipose tissue and muscles [6]. Importantly, dysregulated insulin signaling has been proposed to be associated with PD pathogenesis either triggering or accelerating the pace of the disease development. More specifically, a bulk of data are supporting that T2DM is a risk factor for PD. In a recent systematic review and meta-analysis patient with T2DM had 1.34 higher risk of developing PD accompanied by more severe motor symptoms [7], whereas previous population-based studies showed that T2DM may increase PD risk approximately by 40% [8,9]. In another study this correlation was associated with the duration of T2DM increasing to 1.618 after a duration >5 years [10]. Insulin resistance has also been associated with dopamine degeneration implicating mainly the AKT insulin signaling [11]. Downstream molecules of this pathway such as forkhead box protein O (FoxO), mechanistic target of rapamycin (mTOR) and glycogen synthase kinase 3β (GSK3β) are implicated in processes such as a-synuclein degradation, mitochondrial biogenesis, oxidative stress and inflammation all being of crucial importance in PD pathogenesis. Interestingly, insulin resistance in mice has been associated with altered a-synuclein expression, mitochondrial dysfunction and oxidative stress [12]. In mice treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), caused insulin resistance, neuroinflammation and increased a-synuclein [13]. Moreover, insulin resistance is present in approximately 60% of PD patients with dementia. Altered glucose metabolism is also present in multiple brain regions of PD patients with dementia [14,15] and PD patients with concomitant T2DM are found to have more severe cognitive decline. Interestingly, in a PD rat model the activation of the peroxisome proliferator-activated receptor gamma (PPAR-γ), which increase insulin sensitization and glucose metabolism, protected against MPTP-induced memory impairment [16]. Additionally, in a recent 6-OHDA PD rat model study, intranasal insulin, attenuated motor deficits and improved mitochondrial function [17]. Additionally, in a small RCT, intranasal insulin was also associated with improved cognitive function and Unified Parkinsons Disease Rating Scale (UPDRS) score [18]. All these data indicate that T2DM and PD may have some common pathogenic pathways, intervention on which is a target of intense research during the last years. Interestingly, GLP-1R agonists which have been approved by the FDA for the treatment of T2DM, are recently emerging as promising, therapeutic agents in PD, increasing the expectations for identifying new PD drugs that could possibly be neuroprotective or even halt or reverse disease progression.

3. GLP-1 and GLP-1 Receptor

GLP-1 is an endogenous 30 amino-acid multifunctional peptide produced by proteolytic cleavage of proglucagon molecules and secreted by the distal intestinal ileum and colon L-cells after food intake. GLP-1 is also produced in the CNS, at the neuronal level of the solitary tract within the brainstem. GLP-1 has been shown to affect multiple neuronal functions such neurogenesis, neurodegeneration, energy homeostasis, thermogenesis, blood pressure control, and retinal repair.

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In the pancreas, GLP-1 enhances insulin secretion and synthesis, promotes pancreatic β-cell proliferation and survival and decrease glucagon release as well as β-pancreatic cell apoptosis. GLP-1 can also increase glucose uptake by muscles and enhance lipolysis and glucose uptake in adipocytes. It can also reduce appetite, slow gut emptying and gastric acid secretion. In the kidney it is associated with mild natriuresis. Moreover, GLP-1 increases contractility and heart rate in the heart and has vascular protective effects [19,20]. GLP-1 acts via binding to GLP-1 receptors (GLP1-Rs), which are seven transmembrane-spanning proteins that belong to the class B1G protein-coupled receptor family. GLP1-Rs consist of 463 amino acids and are expressed in pancreatic islet cells, as well as in other organs, such as the gastrointestinal tract, lung, heart, kidney and brain, exerting indirect metabolic actions [21]. In the brain it is expressed in the hypothalamus, the hippocampus, the subventricular zone, the striatum, the substantia nigra, the cortex and the brain stem. GLP-1 has been associated with improved endothelial function, suppression of inflammation and a cardioprotective role, as well. GLP-1 has a short half-life and is inactivated by the enzyme dipeptidyl peptidase IV (DPP-IV), however GLP1-Rs are not cleaved by DPP-IV and can cross the blood brain barrier (BBB), thus they are important candidates for treating brain diseases. Overall, GLP-1 and GLP1-Rs are major components of the gut/brain axis and through the multiple functions that they exert, may be a crucial link between metabolic and brain dysfunction.

4. GLP-1 Receptor Agonists

GLP-1 and GLP1-Rs are known as approved agents for T2DM treatment. However, GLP1-Rs due to their ability to escape inactivation by DPP-IV and to cross the BBB, are promising candidates to treat neurodegenerative disease such as PD. GLP-1R agonists are divided to short-acting and long-acting based on the time-effect and the volume of injections needed [11,20]. Short-acting preparations such as exenatide, are needed to be injected 2-3 times a day, whereas long-acting preparations such as lixisenatide and liraglutide are injected once a day. Long-acting preparations also include drugs such as semaglutide, dulaglutide or long-acting release formulation of exenatide, which generally need to be injected once a week. Exenatide was the first drug used for T2DM treatment. It is a synthetic version of exendin-4, a peptide which shares 53% amino acid sequence with native GLP-1, is resistant to DPP-IV and binds to GLP-1Rs. Exendin has a short half-life, after a subcutaneous injection > 0.2 μg/kg it can be detected in the plasma in about 15 minutes and for approximately 15 hours. Lixisenatide, is also a synthetic peptide derived from the exendin-4 hormone with an increased half-life about 3 hours and an increased binding affinity with the GLP-1R by four times. It has also a slower rate of dissociation from its receptor, thus a prolonged pharmacological effect. A recent longer-lasting pegylated version of exendin-4 (NLY-01) has also been developed. Liraglutide is a GLP-1 recombinant analogue characterized by delayed absorption and extended plasma half-life, over 13 hours, due to binding to albumin. In comparison to short-acting GLP-1R agonists, liraglutide has fewer side effects and a better improvement in lowering glycated hemoglobin as well as fasting blood glucose. Albiglutide, is a recombinant fusion protein consisting of two copies of a 30-amino acids sequence of modified human GLP-1 which also binds to albumin and a half-life of 5 days. Dulaglutide, consists of two DPP-IV-protected GLP analogues covalently linked to a human Ig G4-fragment crystallisable (Fc) heavy chain, produced via recombinant DNA technology. It has a long half-life period and the average peak time of subcutaneous injection is 48 hours. Semaglutide, another GLP-1 analogue has also reduced susceptibility to DPP-IV. In fact, it is a modification of liraglutide with a much-enhanced survival time in the blood. Importantly, dual and triple GLP-1R/Gastric inhibitory polypeptide receptor (GIP-R) agonists have been developed maximizing the beneficial effects and minimizing the adverse effects of these agents. Among the dual GLP-1R/GIP-R agonists, tirzepatide has a high albumin affinity, thus an increased half-life of 5 days. Structurally it is composed of a peptide of 39 amino acids with the bioactive sequence of gastric inhibitory polypeptide (GIP), and with a sequence acting on GLP-1 replacing its intermediate amino acid; other agents are DA-JC1, DA2, DA-CH3, DA-JC4 and DA-CH5. A synthetic monomeric peptide triple receptor agonist, called triagonist that incorporates GLP-1, GIP and glucagon actions has also been found to have neuroprotective effects [11]. In general, the ability of these drugs to protect the brain is directly

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associated with their penetration ability in the brain. Exenatide has been found to have greater ability to cross the blood brain barrier (BBB) compared to liraglutide, lixisenatide and semaglutide. Liraglutide, semaglutide and DA1-JC have been found to show very low penetration of the BBB. Moreover, among dual agonists, DA4-JC and DA5-CH have been shown to penetrate the BBB more effectively, followed by DA3-CH and DA1-JC. NLY01, has been found to hardly crossed the BBB. Agents that can hardly cross the BBB may influence brain function indirectly by affecting other substances that can cross the BBB. Importantly, recent evidence from animal models, preclinical and clinical studies support that GLP1-Rs are a new category of molecules that can hopefully open up new avenues in the field of PD treatment.

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

Intense research on the field of new therapeutic strategies in PD therapy has highlighted GLP1-R agonists as possible novel therapeutic agents. Many data on animal models and preclinical studies show that GLP1-R agonists can restore dopamine levels, inhibit dopaminergic loss, attenuate neuronal degeneration and alleviate motor and non-motor features of PD. Up to now evidence from clinical studies are also very promising enhancing the possibility of adding GLP1-R agonists in the current armamentarium of drugs available for PD treatment.

5.1. Evidence from Animal Models-Preclinical Studies

Novel incretin analogues including exendin-4 were found to improve autophagy and protect from mitochondrial stress induced by a toxic mitochondrial complex I inhibitor, rotenone in dopaminergic SH-SY5Y neuroblastoma cells, increasing the survival of SH-SY5Y cells [22]. Peripheral administration of GLP-1R agonists increased the expression of tyrosine hydroxylase (TH)-containing neurons [23]. TH is core enzyme in the pathway of dopamine synthesis. Exenatide was also found to protect dopaminergic neurons towards 6-OHDA and MPTP toxicity, increasing dopamine levels and improving motor abilities in diabetic rats with MPTP induced PD [24–28]. Moreover, continuous exendin-4 administration had a protective effect on cognitive-related neurotransmission systems and decreased the death of hippocampal neurons induced by injection of toxin lipopolysaccharide in mice [29]. In a parkinsonian rat model of α-synucleinopathy, exendin-4 alleviated TH-positive neuronal loss and terminal denervation, affected the expression of a functional component of monoaminergic neurotransmission, vesicular monoamine transporter 2, in the nigrostriatal dopaminergic systems of rats, and improved motor symptoms [30]. In another mouse model a modified form of exenatide (NLY01) protected against the loss of dopaminergic neurons [31]. Interestingly, in a comparison dual agonist DA5-CH and NLY01 MPTP mouse model study, the dual agonist was found to be more effective compared to NLY01, regarding PD pathology [32]. A sustained- release exenatide agent, PT302 was found to sustain dopaminergic neurons after 6-OHDA lesioning in rats, however this result was not replicated in another study [33,34]. Interestingly, in a recent study, in a PD mouse model, early treatment with PT320 ameliorated L-DOPA-induced dyskinesia, highlighting its possible denervation effect [35]. Notably, in another study lixisenatide and liraglutide were found to be more effective regarding protection against MPTP-induced dopaminergic degeneration compared to exenatide [36], however these results need to be replicated [37]. In a recent MPTP PD mouse study, both exendin-4 and linagliptin reversed motor dysfunction, glial activation, and dopaminergic neuronal death [38]. Interestingly, once weekly administration of semaglutide was more efficient compared to once-daily liraglutide in restoring TH levels in MPTP-treated mice [39,40]. Neuroprotective effects were also observed for a novel GLP-1 analogue with a longer serum half-life than exendin-4, Val(8)GLP-1-GluPal in a mouse MPTP PD model [41]. Moreover, in a rotenone model of PD, sitagliptin and liraglutide improved motor performance, reversed rotenone-induced nigral neuronal loss, inhibiting the inflammatory-apoptotic degenerative process [42,43].

Regarding dual GLP-1/GIP receptor agonists, DA-JC1 has been observed to have a neuroprotective effect in a MPTP mouse model [44–46], as well as in a cell culture experiment, in SH-SY5Y cells with ROT-induced mitochondrial stress [22] which was also superior to older GLP-1 analogs [47]. In another MPTP mouse study, DA3-CH was better compared to liraglutide in rescuing

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TH levels [48]. In a recent study, DA5-CH was more effective compared to semaglutide regarding the protection of dopaminergic neurons, the suppression of inflammation and the increase in TH expression in the substantia nigra. Aggregation of a-synuclein was reduced by both drugs, as well as insulin resistance with DA5-CH displaying better results [49]. In ROT-lesioned rats the dual GLP-1R/GIPR agonist could improve motor symptoms of PD, too [50]. In a comparison MPTP PD mouse model study comparing liraglutide with DA-JC1, DA-JC4 and DA-CH5 at the same dose, DA-JC4 and DA-CH5 were most effective [51,52]. Moreover, DA-CH5 was found to be more effective compared to NLY01, as well in suppressing neurodegeneration and inflammation [53].

5.2. Evidence from Clinical Studies

A number of clinical studies have already been conducted regarding GLP1R agonists and PD and the initial results are very promising, regarding the effect of these drugs in the improvement of PD pathology (Table 1).

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

ClinicalTrial.gov Identifier	Drug	Result	Reference
NCT01174810	Exendin-4	Improvement of MDS-UPDRS and Mattis DRS-2	[54]
NCT01971242	Exendin-4	Improvement of MDS-UPDRS	[55]
NCT02953665	Liraglutide	improvement in daily living of PD patients	[56]
NCT03439943	Lixisenatide	Improvement in MDS-UPDRS III	[57]

In a randomized, single-blind, open-label trial (NCT01174810) [54], exendin-4 was administered twice a day in 45 PD patients with moderate disease, for 1 year. The patients were on conventional PD treatment. PD patients without taking this agent were considered as controls. In this study there was a 2-month wash-out period. After 14 months, there was a significant difference in motor and cognitive function measured by Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS) and Mattis dementia rating scale-2 (Mattis DRS-2), respectively. These beneficial results were sustained in the follow-up assessment after a wash-out phase of 12-weeks [58]. The untreated control group rapidly deteriorated in the same time period, highlighting the disease-modifying properties of exendin-4.

Due to these positive results a randomized, double-blind, placebo-controlled phase II clinical study (NCT01971242) [55], was conducted by the same research team in 60 PD patients with moderate disease with subcutaneous administration of exendin-4, 1 injection /week for 48 weeks. The patients were on conventional PD treatment. In this study there was a wash-out period of 12-weeks. The PD patients that were administered exendin-4 had better motor control in comparison with the placebo group, after 48 weeks of drug therapy and these results was retained after 60 weeks. A post-hoc analysis showed that non-motor signs, such as 'emotional well-being' and mood/apathy scores, were also better in PD patients on exenatide treatment but these results were not sustained after discontinuation of therapy [59]. An additional post-hoc analysis also showed that obese PD patients or with insulin resistance may have better cognitive results to exenatide in comparison to other PD subgroups [60]. Interestingly, neuronal derived exosomes from patients that participated in this phase II trial had higher levels of Insulin receptor substrate 1 (IRS-1) phosphorylation at tyrosine sites and higher levels of phosphorylated mTOR and phosphoinositide-3-kinase/Akt (PI3K/AKT) expression in PD patients treated with exenatide compared to the placebo group [61].

A randomized, double-blind, phase II clinical trial was also conducted regarding the effect of liraglutide in PD patients (NCT02953665). In this study, 37 active and 18 placebo subjects were included. Subcutaneous injections of liraglutide were administered for 52 weeks in PD patients who were on conventional PD treatment. This study documented significant improvement in daily living of PD patients that were on liraglutide treatment [56]. Further parameters are still being analyzed.

In another randomized, double-blind, placebo-controlled clinical trial (NCT03439943), lixisenatide was administered daily for 1 year in PD patients with early stage of the disease. Patients were examined both during OFF and ON times. PD patients on lixisenatide treatment showed less

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disability on the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) and this improvement was eminent in ON and OFF times [57].

Other clinical trials examining the effect of semaglutide (NCT03659682), liraglutide (NCT02953665), NLY01 (NCT04154072), or PT320 (NCT04269642), exendin-4 (NCT04305002) and (NCT04232969) in PD patients, are also ongoing are results are awaited.

5.3. Mechanism of Action

PD is a heterogenous neurodegenerative disease with complex aetiology. Multiple pathways have been implicated in PD pathogenesis such as protein misfolding and aggregation, defects in the ubiquitin–proteasome system and aggregation, inflammation, impaired oxidative stress and mitochondrial dysfunction. Current evidence indicates that GLP-1Rs affect multiple of these pathways.

In in vitro and in vivo studies, exendin-4 prevented the activation of glial cells, restricting neuroinflammation and neurodegeneration [38,62–64]. Also, GLP-1 had anti-inflammatory effects in models with LPS induced lesions [62,65]. Moreover, in a parkinsonian rat model of α-synucleinopathy, exenatide-4 decreased levels of TNF-α and IL-1β in a dose-dependent way [66], as well as in lesions induced by 6-OHDA [66], and ROT [28]. In other studies, exendin-4 was found to decrease IL-6 levels, as well as NF-kB and cyclooxygenase1 (COX1) all of which are important mediators of inflammation [29,67]. Liraglutide and sitagliptin have been observed to decrease microglial activation and inflammation in ROH-treated rats, too [42,43]. In a mouse MPTP model of PD, liraglutide has been suggested to exert its neuroprotective effects against inflammation via the AMP-activated protein kinase (AMPK)/NF-κB pathway [68]. Novel GLP-1/GIP receptor dual agonists have also been shown to affect microglia activation and levels of pro-inflammatory cytokines [52,69].

Except for inflammation, GLP-1Rs have been found to affect oxidative stress and mitochondrial homeostasis, as well. In rodents with 6-OHDA and ROT-induced lesions, GLP-1R was associated with increased expression of B-cell lymphoma-2 (Bcl-2) and complex I and reduced expression of caspase-3, halting cell death [70,71]. In 6-OHDA- treated SH-SY5Y cells, exendin-4 and DA-CH5 reduced ROS levels, too [47]. GLP-1 has been suggested to decrease oxidative stress via receptor-mediated stimulation of the cyclic AMP, PI3K, and protein kinase C pathways and activation of nuclear factor erythroid 2-related factor 2 (Nrf-2) [72]. Moreover, in mice treated with MPTP, liraglutide has been observed to increase peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) levels and increase NRF2 expression, aiding mitochondrial regeneration [73].

Regarding the implication of GLP-1RA in the process of protein folding, liraglutide has been shown to decrease MPTP-induced α-syn aggregation in mice [74]. Exendin-4 was also associated with increased clearance of total α-syn and pathological pSer129-α-syn via autophagy in the substantia nigra pars compacta of rats, probably via suppression of the PI3K/Akt/mTOR signaling pathway [75]. NLY01 has been shown to affect aggregation of α-syn in dopamine neurons, too [76].

DA-CH5 and exendin-4 have been shown to increase the expression of sequestosome-1 and Beclin-1, affecting also the process of autophagy [47]. Exendin-4 has been observed to increase anti-apoptotic proteins, phospho-Bcl-2 (Ser70) and phospho-BAD (Ser112), and reduce the pro-apoptotic protein Bax, and inhibit caspase-3 activity, as well [22,77]. Notably, in rat 6-OHDA models, DA-CH5 and exendin-4 have been suggested to exert their neuroprotective by inducing autophagy and inhibiting apoptosis, particularly by enhancing autophagic activity and reducing the Bax/Bcl-2 and active-caspase-3/caspase-3 ratios [22]. Downregulation of apoptotic pathways, including poly (adenosine diphosphate (ADP) ribose) polymerase (PARP) and activation of the PI3K/Akt signaling pathway has also been observed [78]. GLP-1 mimetics have also been found to increase autophagy by promoting the expression of autophagy related 3, autophagy related 7 and LC3A/B in SH-SY5Y cells with ROT-induced mitochondrial damage [79]. In AAV-A53T-α-rats exendin-4 also enhanced autophagy increasing the expression of LC3-II and down-regulating mTOR and Akt [30]. In a mice MPTP model, liraglutide affected levels of fission and fusion mitochondrial proteins, restoring mitochondrial morphology [73,74]. In a recent study in SH-SY5Y cells treated with 6-OHDA, both

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semaglutide and liraglutide protected against 6-OHDA cytotoxicity by increasing autophagy flux and decreasing oxidative stress as well as mitochondrial dysfunction, with semaglutide being superior compared to liraglutide [80].

6. Conclusions

PD is a common neurodegenerative disease which current treatment is limited in the symptomatic relief of patients. Interestingly, recent data suggest that dysregulated insulin signaling may be associated with PD, insulin resistance may be implicated in dopamine degeneration and altered glucose metabolism is present in multiple brain regions of PD patients. In line with these data, T2DM has been observed to be a risk factor for PD. Interestingly, GLP-1R agonists which have been approved by the FDA for the treatment of T2DM, are recently emerging as promising, therapeutic agents in PD. Many data on animal models and preclinical studies show that GLP1-R agonists can restore dopamine levels, inhibit dopaminergic loss, attenuate neuronal degeneration and alleviate motor and non-motor features of PD. Clinical studies regarding the role of GLP1-R agonists, such as exendin-4, liraglutide and lixisenatide in PD also show improvement in motor and cognitive functions, as well as in daily living parameters of these patient, reinforcing the ambition to identify novel PD modifying agents. GLP1-R agonists have been proposed to affect neuroinflammation, oxidative stress and mitochondrial homeostasis, protein folding, autophagy and apoptosis, pathways that have been already been implicated in PD pathogenesis. The results of a number of clinical trials are also awaited to be available soon, aiming to achieve the challenging but also feasible goal to halt or even reverse progression of this devastating disease.

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