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Review

Parkinson's disease and diabetes mellitus: common mechanisms and treatment repurposing

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From the Contents

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Abstract

In the last decade, attention has become greater to the relationship between neurodegeneration and abnormal insulin signaling in the central nervous system, as insulin in the brain is implicated in neuronal survival, plasticity, oxidative stress and neuroinflammation. Diabetes mellitus and Parkinson's disease are both aging-associated diseases that are turning into epidemics worldwide. Diabetes mellitus and insulin resistance not only increase the possibility of developing Parkinson's disease but can also determine the prognosis and progression of Parkinsonian symptoms. Today, there are no available curative or disease modifying treatments for Parkinson's disease, but the role of insulin and antidiabetic medications in neurodegeneration opens a door to treatment repurposing to fight against Parkinson's disease, both in diabetic and nondiabetic Parkinsonian patients. Furthermore, it is essential to comprehend how a frequent and treatable disease such as diabetes can influence the progression of neurodegeneration in a challenging disease such as Parkinson's disease. Here, we review the present evidence on the connection between Parkinson's disease and diabetes and the consequential implications of the existing antidiabetic molecules in the severity and development of Parkinsonism, with a particular focus on glucagon-like peptide-1 receptor agonists.

Key Words: antidiabetic; diabetes mellitus; dopamine; exenatide; glucagon-like peptide-1; insulin; neurodegeneration; neuroinflammation; Parkinson's disease; repurposing

Introduction

Diabetes mellitus (DM) and Parkinson's disease (PD) are disorders associated with aging, and their prevalence is increasing worldwide. DM is a well-known epidemic in modern society. Among neurodegenerative disorders, PD is the second most frequent and is the fastest growing neurological disease. The number of affected individuals since 1990 has doubled, and this trend is expected to continue rising for the next 30 years (GBD 2016 Parkinson's Disease Collaborators, 2018). It is widely accepted that the etiology of PD is multifactorial and that we must approach all the available strategies to fight against neurodegeneration. In recent years, the role of DM in neurodegeneration has grown special interest not only as a contributing factor to disease onset but also as a modifying factor of motor and nonmotor symptoms. The influence of a widespread condition such as DM on the prognosis of PD opens a door to the possible use of antidiabetic medications in the battle against PD. Here, we performed a PubMed database literature review of articles published in English, Spanish, Portuguese or French from inception up to May 2021, combining the search terms of Parkinson, dopamine, diabetes, antidiabetic, repurposing and each of the antidiabetic medications. We also revised references of eligible articles.

Parkinson's Disease and Diabetes Mellitus

A first step to understand the connection between DM and PD is to analyze the epidemiological evidence. Two relevant meta-analyses have been published in the last decade evaluating the evidence in this area. The first meta-analysis in 2011 resolved that in prospective studies, DM constituted a risk factor for PD (risk ratio [RR] = 1.37, 95% confidence interval [CI]: 1.21–1.55; $P < 0.0001$; Cereda et al., 2011). A second study in 2016 included seven cohort studies with over 1.7 million individuals and concluded that the risk for PD in diabetic patients was enhanced by approximately 38% (RR = 1.38; 95% CI: 1.18–1.62; $P < 0.001$) and that this risk was higher when diabetes duration was under 10 years and in women (females RR = 1.50; 95% CI: 1.07–2.11; *vs.* males RR = 1.40; 95% CI: 1.17–1.67; Yue et al., 2016). An increased risk in female patients was observed in other studies despite male preponderance in PD (GBD 2016 Parkinson's Disease Collaborators, 2018), especially in subjects aged 40–79 years (odds ratio (OR) = 1.71; 95% CI: 1.60–1.82, $P < 0.001$; RR = 1.17; 95% CI: 1.11–1.30) and in females older than 80 years (OR = 1.39; 95% CI: 1.33–1.46; $P < 0.001$; RR = 1.09, 95% CI: 1.01–1.18; Deischinger et al., 2021). We hypothesize that this fact may be related to the protective role of sex steroids such as 17β-estradiol on the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular-signal-regulated kinase (MAPK/ERK) pathways. Nonetheless, in the Neurological Disorders in Central Spain study (De Pablo-Fernandez et al., 2017), the relationship found between DM and PD was not statistically significant (OR = 1.89, 95% CI: 0.90–3.98, $P = 0.09$); however, subjects with long-duration diabetes (more than 10 years) showed a significantly positive association (OR = 3.27; 95% CI: 1.2 –8.85; $P = 0.02$). These previous studies included patients with type 2 DM (T2DM), and the existing data regarding the risk of type 1

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DM (T1DM) patients are limited. In a nationwide large claims dataset study in Austria (Klimek et al., 2015) with a 1.8 million individual cohort, an association between PD and DM was observed for T1DM (RR = 2.3; 95% CI: 1.9–2.7) and T2DM (RR = 1.5; 95% CI: 1.4–1.6). Nonetheless, this study included only individuals with inpatient stays, so possible selection bias may be present. Data from genome-wide association studies (Witoelar et al., 2017) showed weak associations between type 1 diabetes and PD, so the elevated risk in type 1 DM may be due to a longer duration of disease and not to different factors, such as autoimmune or genetic agents. To clarify the possible effect regarding DM disease duration, a large-scale Korean cohort including over 15 million subjects analyzed the PD risk in four groups of participants: nondiabetic, impaired fasting glucose, diabetes less than 5 years duration, and diabetes of more than 5 years duration (Rhee et al., 2020). PD risk significantly increased with the duration of diabetes and hyperglycemia (DM < 5 years hazard ratio (HR) = 1.185; 95% CI: 1.143–1.229; and DM ≥ 5 years HR = 1.618; 95% CI: 1.566–1.672) and was also greater for patients with impaired fasting glucose (HR = 1.038; 95% CI: 1.009–1.067).

In a nested case-control study (Pagano et al., 2018) including 78 subjects followed for three years, T2DM was associated with faster progression and worsening of motor scores, diminished striatal levels of dopamine transporter (DAT) binding, higher levels of tau in the cerebrospinal fluid and higher cognitive deterioration in PD patients. Moreover, non-PD diabetic patients presented less striatal DAT binding and an increase in cerebrospinal fluid levels of alpha-synuclein and tau relative to healthy individuals. However, the group of subjects with DM and PD had an older age and longer disease duration, and the potential effect of diabetes severity or duration was not assessed. Another case-control study, which followed a total of 178 patients over 3 years (Cereda et al., 2012), observed that patients with DM (97.8% T2DM) prior to PD onset presented worse severity scores in the motor and activities of daily living sections of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), together with more advanced stages of Hoehn-Yahr, and needed a larger L-dopa dosage (adjusting the groups for disease duration). A recent publication (Ou et al., 2021) confirmed these findings but only in patients with poorly controlled T2DM, although this group had older age, older age of onset and worse cognitive function.

Amylin

Another link between DM and neurodegeneration is amylin. Amylin or islet amyloid polypeptide is secreted by beta-cells in the pancreas after elevations of blood glucose with insulin. Amylin can aggregate in nonpancreatic tissues and be toxic and has crossed reactions with different amyloidogenic proteins, such as amyloid-beta (Aβ). Amylin can cross the blood-brain barrier (BBB) and reach the amylin receptor, which is a calcitonin receptor vastly expressed in the brain (Boccia et al., 2020) and correlates with regions with important amyloid-beta burden (basal forebrain, hippocampus, cortex) (Jhamandas et al., 2011). The amylin receptor displays different physiological functions, including regulation of dopamine signaling (Mietlicki-baase et al., 2014), and has been proposed to be neuroprotective in different animal models. On the other hand, amylin in animal models does not share neurotoxicity with Aβ in cultures, especially in human hippocampal neurons, and its aggregation properties are stronger in humans (Lim et al., 2008). This fact suggests that further research is needed on the role of amylin in neuroprotection and the possible neurotoxicity of the human amylin analogue pramlintine, which is used in the treatment of DM.

Furthermore, Aβ can also activate amylin receptors, and this activation leads to neurotoxic and apoptotic effects that imply the same group of proteins in the mitochondria, especially related to complex IV activity and respiration. Importantly, amylin in the brain not only cross-reacts with Aβ but also with α-synuclein. Moreover, mixing monomers of α-syn and amylin accelerates coaggregation, triggering amyloid α-synuclein formation (Horvath and Wittung-Stafshede, 2016), exacerbating the PD risk in T2DM. This increased deposition has been observed in cellular (Mucibabic et al., 2020) and animal models (Sun et al., 2020), as well as in pathological studies in humans (Martinez-Valbuena et al., 2018). Therefore, inhibition of amylin-induced aggregation may be an aim to reduce the formation of α-synuclein and Aβ. Conversely, a recent neuropathological study in 25 PD patients with pre-existing T2DM reported that diabetic individuals suffered a more aggressive phenotype, but this was not related to characteristics known to be associated with a more severe disease, such as enhanced Lewy pathology, cerebrovascular load, or Alzheimer's disease pathology (de Pablo-Fernández et al., 2021).

Treatment Repurposing

After considering the evidence of the association of DM and neurodegeneration and contemplating that they share common pathological mechanisms, it is reasonable to weigh the possible capability of DM medications to modify PD disease progression. A longitudinal cohort study reported a higher risk of PD in untreated T2DM patients (Brauer et al., 2020), as well as a different PD incidence among T2DM subjects depending on the antidiabetic medication administered. Therefore, it is of great interest to assess the possible repurposing of existing antidiabetic molecules in neuroprotection, especially in PD (**Figure 1** and **Table 1**).

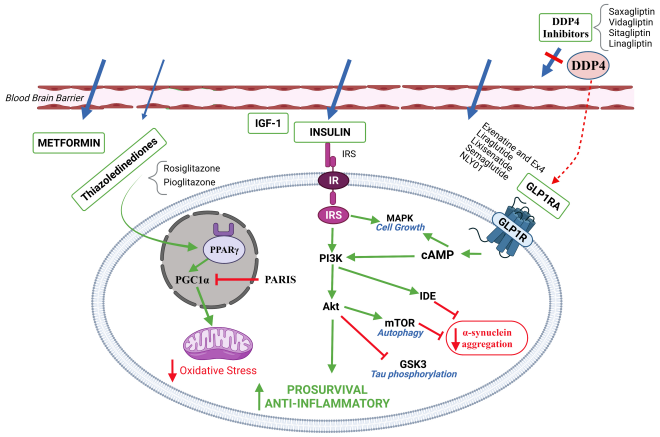

Figure 1 | **Mechanisms induced by antidiabetic drugs leading to anti-inflammatory and prosurvival effects in dopaminergic neurons.**
Blue arrows indicate blood-brain barrier penetration. Green arrows indicate activatory/beneficial effects. Red lines indicate inhibitory effects. Akt/PKB: Protein kinase B; DDP4: dipeptidyl-peptidase 4; GLP1R: glucagon-like peptide-1 receptor; GLP1RA: glucagon-like peptide-1 receptor agonists; IDE: insulin degrading enzyme; IGF-1: insulin-like growth factor-1; IR: insulin receptors; IRS: insulin receptor substrates; MAPK: mitogen-activated protein kinase; mTOR: mammalian target of rapamycin; PGC1α: peroxisome proliferator activated receptor gamma coactivator 1-alpha; PI3K: phosphatidylinositol 3-kinase; PPARγ: peroxisome proliferator-activated receptor gamma. Created with BioRender.

Insulin

Brain cells do not require insulin for glucose uptake. Insulin in the brain not only has metabolic functions but is also involved in cell growth, cognition, behavior or neuroprotection, among others. It can be locally secreted by serotoninergic signaling in the choroid plexus (Mazucanti et al., 2019). Insulin is able cross the BBB via saturable receptor-mediated transport that can be repressed by obesity, prolonged peripheral hyperinsulinemia or aging (Blázquez et al., 2014).

Insulin binds to the insulin receptor (IR), which is widely present in the brain, and IR substrates (IRS) 1 and 2 are phosphorylated. This activates two principal pathways: the phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK/ERK) pathways. PI3K triggers the activation of the mammalian target of rapamycin (mTOR) and the protein kinase-B (PKB/Akt) branches. Akt is an essential modulator of cellular processes and is able to phosphorylate more than fifty downstream proteins that regulate vital functions, such as mitochondrial biogenesis, apoptosis, inflammation or autophagy, that determine dopaminergic cell survival (Fiory et al., 2019). In addition to the PI3K pathway, insulin can also regulate mitochondrial function via the peroxisome proliferator activated receptor gamma coactivator 1-alpha (Parkin/PARIS/PGC1α) pathway. Insulin resistance and T2DM lead to low levels of Parkin and PGC1α, which control mitochondrial proteins and genome expression and downregulate polo-like kinase-2, which increases reactive oxygen species production and abnormal mitochondrial metabolism (Hong et al., 2020). Mitochondrial respiration is also impaired by elevated intraneuronal glucose concentrations, inducing the creation of reactive oxygen species, producing cell damage and forming precursors of advanced glycation end products (AGEs) that alter protein and lipid functions and

Table 1 | **Summary of human clinical data involving the effects of anti-diabetic treatments in Parkinson's disease**

Treatment	Reference	Results
Exenatide	Aviles-Olmos et al., 2013	Single-blind, 12 mon, Exenatide trial in 45 PD patients
		Significant benefit in motor (4.9 points difference, 95% CI: 0.3–9.4; *P* = 0.037) and cognitive (6.3 points difference, 95% CI: 2.7–9.9; *P* = 0.001) symptoms
	Aviles-Olmos et al., 2015	Extended 24 mon follow-up of previous trial
		Confirmation of neuroprotective role of Exenatide in cognitive (5.3 points difference, 95% CI: 9.3–1.4; *P* = 0.006) and motor symptoms (5.6 points difference, 95% CI: 2.2–9.0; *P* = 0.002)
	Athauda et al., 2017	Double-blind, placebo-controlled, 48 wk treatment and 12 wk washout period
		Improvement with Exenatide of motor-symptoms (mean difference of –3.5 points, 95% CI: –6.7 to –0.3; *P* = 0.0318) that persisted after the washout period
	Athauda et al., 2018	Non-motor and cognitive analysis of previous trial
		A 3.7 times (95% CI: 27.0–0.51; *P* = 0.198) lower likelihood of suffering cognitive impairment in the Exenatide group
	Athauda et al., 2019a	Study of Akt pathway and brain insulin activity using biomarkers for neuronal-derived exosomes
		Higher IRS1 phosphorylation and Akt and mTOR expression were found in Exenatide group associated to better motor scores.
	Athauda et al., 2019b	*Post hoc* analysis
		Better results of Exenatide were found in patients with tremor-dominant phenotype and lower MDS-UPDRS-2 scores, lower benefits were found in patients aged > 65 yr.
	Wang et al., 2020	Meta-analysis
		Exenatide improves motor and non-motor symptoms, also cognitive function and UPDRS IV scale.
	Mulvaney et al., 2020	Cochrane Meta-analysis
		Light benefit in motor symptoms (mean difference –3.10, 95% CI: –6.11 to –0.09) and uncertain results regarding non-motor and cognitive function
DDP4 inhibitors	Svenningsson et al., 2016	Case-control study (Vildagliptin, Sitagliptin, Saxagliptin)
		DPP4 inhibitors were related with low PD incidence (OR = 0.23, 95% CI: 0.07–0.74).
	Brauer et al., 2020	Longitudinal cohort study
		DDP4 inhibitors were associated with a risk reduction in PD incidence (IRR = 0.64; 95% CI: 0.43–0.88; *P* < 0.01).
	Jeong et al., 2021	Retrospective study
		Improvement in motor symptoms and increased dopamine transporter availability in DDP4 group
Metformin	Ping et al., 2020	Meta-analysis
		Increased PD incidence (OR = 1.66; 95% CI: 1.14–2.42)
Thiazoledinediones	Hussain et al., 2020	Meta-analysis
		Decrease of PD incidence (HR = 0.81; 95% CI: 0.70–0.93), especially when > 5 yr (HR = 0.74; 95% CI: 0.62–0.88)
Pioglitazone	NINDS trial, 2015	Prospective trial
		No significant decline of PD incidence was observed.
	Chang et al., 2020	Retrospective study
		Reduction of PD incidence with pioglitazone increased when combined with statins.
	Brauer et al., 2020	Prospective cohort study
		No significant effects regarding PD incidence
Ongoing clinical trials	NCT04232969	Exenatide-PD3 trial
		Exenatide weekly during 2 yr in PD patients
	NCT03456687	Phase I, EudraCT 2019-000732-26
		Exenatide weekly during a year in PD patients
	NCT04154072	Phase II trial
		NLY01 (Pegylated Exenatide) in early untreated PD patients
	NCT04269642	Phase IIa trial
		PT320 (extended release Exenatide formulation) in early PD patients.
	NCT02953665	Phase II, double-blinded, placebo-controlled trial
		Liraglutide once daily during 14 mon, analysing non-motor symptoms and motor changes
	NCT03659682	Double-blind, placebo-controlled
		Semaglutide during 2 yr, in early PD patients
	NCT03439943	Double-blind, placebo-controlled, parallel group, phase II
		Lixisenatide during 12 mon in early PD patients

Akt: Protein kinase B; CI: confidence Interval; DPP4: Dipeptidyl peptidase-4; HR: Hazard ratio; IRR: Incidence rate ratio; IRS-1: Insulin receptor substrate 1; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; mon: Months; mTOR: mammalian target of rapamycin; OR: odds ratio; PD: Parkinson´s Disease; wk: weeks; yr: years.

promote oxidative stress, neuroinflammation and neuron death (Chen et al., 2017). AGEs are present in the Lewy body periphery and are increased in α-synucleinopathies. Neurons with elevated energy requirements, such as dopaminergic neurons, are more exposed to dysfunctional mitochondrial metabolism and therefore more vulnerable to hyperglycemia. This heightened susceptibility of nigral neuron cells to damage by diabetes has been described in animal (Pérez-Taboada et al., 2020) and *in vitro* models (Juárez-Flores et al., 2020). AGEs can also react with methylglyoxal (MG), which is a glycolytic byproduct that can target many functional sites of proteins. MG reacts with α-synuclein to form oligomers and increase toxicity. Moreover, synergistic toxic effects of MG and α-synuclein have been observed in mouse models (Vicente Miranda et al., 2017). MG is increased in T2DM, and dopaminergic neurons have high glucose metabolism, leading to an elevated vulnerability of nigrostriatal cells in diabetic individuals (Biosa et al., 2018). Animal models of NIRKO

mice (neuron-specific insulin receptor knockout) show decreased dopamine signaling in the striatum and nucleus accumbens due to altered mitochondrial monoamine oxidase A and B activity. These animals showed abnormal depressive and anxiety behaviors that recovered with normal insulin signaling (Kleinridders et al., 2015). Insulin-like growth factor 1 can also bind to IR in the brain and is involved in neuroprotective functions, although its possible use as a therapy is unclear (Labandeira-Garcia et al., 2017).

The role of insulin in neuroinflammation is not limited to neuronal cells. The PI3K/Akt pathway has been reported to induce the M2 anti-inflammatory state and inhibit the M1 proinflammatory state in microglia, as well as to increase A2 and reduce the A1 phenotypes in astrocytes. These changes reduce oxidative stress and facilitate cell survival and neuroprotection (Iravanpour et al., 2021).

Insulin and PI3K also modulate α-synuclein expression and aggregation by activating insulin-degrading enzymes. Insulin-degrading enzymes are zinc metalloendopeptidases that destroy amyloidogenic proteins, and their binding to α-synuclein oligomers can avoid aggregation fibers (Sharma et al., 2015). Moreover, insulin is involved in Aβ production, and Aβ downregulates insulin, hypothesizing that decreased insulin signaling may be the result of Aβ aggregation or a neuroprotective response (Steculorum et al., 2014). PI3K activation by insulin represses glycogen synthase kinase 3 and can also reduce tau phosphorylation. Superimposed tau or Aβ pathology and its interaction with α-synuclein are very relevant for cognitive decline in PD patients.

Insulin regulates vesicular monoamine transporter 2 (VMAT2), which takes up dopamine into presynaptic vesicles, controlling dopamine toxicity. VMAT2 is expressed in both dopaminergic neurons and β cells. VMAT2 expression has been linked to the severity of PD symptoms and sensitization to apomorphine and is reduced in T2DM (Kong et al., 2020).

Dopamine D2-like receptors are present in the pancreas, and dopamine is excreted with insulin vesicles by pancreatic beta cells. The activation of D2 receptors reduces glucose-stimulated insulin release, counteracting the incretin effect of glucagon-like peptide-1 (GLP1) and gastric inhibitory polypeptide or glucose-dependent insulin releasing polypeptide (GIP) (Maffei et al., 2015). Dopaminergic and antidopaminergic medications may influence glucose metabolism via the pancreatic D2 receptor.

In summary, insulin and IR regulate vital neuronal functions for cell survival, primarily via the PI3K pathway. Hyperglycemia impairs mitochondrial respiration and leads to the production of AGEs. Dopaminergic neurons are especially exposed to glucotoxicity due to their greater energetic demands. Therefore, therapies targeting the insulin receptor in the central nervous system can be crucial not only in diabetic individuals but also in individuals with nondiabetic PD. The use of intranasal insulin was studied in animal PD models, and intranasal Humulin ameliorated motor impairment and dopaminergic neuron death, improved mitochondrial function and restrained microglial and astrocyte activation (Iravanpour et al., 2021).

Glucagon-like peptide-1 receptor agonists

GLP1 is produced by intestinal L cells in response to food intake to enhance insulin excretion by the pancreas. However, GLP1 is locally produced in the brain, especially by hypothalamic neurons, and GLP1 receptors (GLP1R) are widely expressed in the human central nervous system (Farr et al., 2016). GLP1R triggers cyclic adenosine-monophosphate (cAMP)-dependent PI3K/Akt and PKA/MAPK pathway activation, which are involved in the modulation of mitochondrial function, glucose homeostasis, apoptosis and other processes, such as inflammation, satiety, memory, synaptic plasticity neurogenesis and stress response (Kim et al., 2017). GLP1 is quickly eliminated by dipeptidyl-peptidase 4 in 2 minutes, so longer duration GLP1R agonists (GLP1RA) are necessary, such as Exenatide (2.4 hours), Liraglutide (13 hours), Lixisenatide (3 hours) or Semaglutide (7 days). Exenatide is synthetized from exendin-4 (Ex4), which is a natural GLP1-like peptide. GLP1RA can be safely used by nondiabetic individuals (Vella et al., 2002), and most of them are able to cross the BBB (except albiglutide and dulaglutide) (Muscogiuri et al., 2017). GLP1RA brain effects are independent of their effect on glycemic control (Filchenko et al., 2018), and intranasal administration and GLP1RA nanoformulations were suggested to improve penetration of the BBB (Mousa and Ayoub, 2019). Microglia and astrocytes can also secrete GLP1 and express GLP1R, whose activation induces the M2 anti-inflammatory state. GLP1 decreases the release of TNFα-related cytokines, modulating inflammatory microglia and leading to the activation of reactive phenotypes of astrocytes that cause neuroinflammation and neuronal loss. NLY01 is a GLP1RA that has proven in experimental models to be effective in blocking the microglial activation of reactive astrocytes, avoiding neuronal death although not directly protecting neurons (Yun et al., 2016). Other incretin analogues have shown beneficial effects not only by protecting dopaminergic neurons but also by reducing astrocyte activation and the release of proinflammatory cytokines (Yuan et al., 2017; Zhang et al., 2021).

Different studies in PD animal models have shown that Ex4 ameliorates dopaminergic neuron loss (Rampersaud et al., 2012; Elbassuoni and Ahmed, 2019) and even promotes neurogenesis (Bertilsson et al., 2008), improving motor and cognitive function. These effects are mediated via GLP1R, and it has been demonstrated that GLP1R knockout animals have no benefits with treatment (Li et al., 2009). Due to the short half-life of Ex4 (2.4 hours), other GLP1RAs have also been studied with favorable results in parkinsonian animal models, such as Ex4 extended release formulations (Chen et al., 2018), lixisenatide (Liu et al., 2015), semaglutide (Zhang et al., 2019) or liraglutide (Palleria et al., 2017; Ma et al., 2019). Moreover, the results in animal models with Ex4 (Abuirmeileh et al., 2012) and liraglutide (Badawi et al., 2019) also suggest that GLP1RA may have a synergistic effect with levodopa, allowing inferior doses with fewer adverse effects and improving the control of dyskinesia.

After promising results in animal models and experimental data, further studies in humans were necessary to determine whether existing treatments for DM were able to change disease progression in PD patients. First, a single-blind trial using exenatide for 12 months with 45 non-DM PD patients was developed as a proof of concept (Aviles-Olmos et al., 2013). The exenatide-treated patients had a significant improvement (2.7 points; SD 7.7) in the "off medication" MDS-UPDRS part 3 scale, while the control group had a worsening of 2.2 (SD 7.3) points, with a 4.9 points (95% CI: 0.3–9.4; P = 0.037) total difference. Interestingly, benefits persisted after the 2-month washout period, with a difference of 4.4 points (95% CI: 0.2–8.7; P = 0.042). Moreover, other positive effects were observed in cognitive function (Mattis dementia rating scale-2 difference 6.3 points; 95% CI: 2.7–9.9; P = 0.001), and the most frequent side effect was weight loss. After these results, participants were followed-up for up to 24 months (Aviles-Olmos et al., 2015), showing that both cognitive and motor benefits were still observed in the exenatide-treated patients. Exenatide-treated patients sustained a 5.6-point (95% CI: 2.2–9.0; P = 0.002) difference in the MDS UPDRS-3 scale and an advantage of 5.3 points (95% CI: 9.3–1.4; P = 0.006) in the Mattis dementia rating scale, supporting the neuroprotective effects of exenatide and discarding a placebo or symptomatic effect of the treatment. However, patients suffered loss of weight together with worsening dyskinetic responses at 12 and 14 months, which were higher than those of controls despite adjusting their levodopa doses (Aviles-Olmos et al., 2015).

This work permitted the development of a randomized, placebo-controlled, double-blind trial to investigate the role of exenatide in PD (Athauda et al., 2017). A total of 62 PD non-DM individuals were included and evaluated 48 weeks later and then after a washout period of 12 weeks. The exenatide group presented a 1-point improvement (95% CI: 2.6 to 0.7) and showed a –3.5-point (–6.7 to –0.3; P = 0.0318) mean difference in the MDS-UPDRS-3 scale (with "off medication"). These benefits remained after the washout period and were even higher than those at the 48-week visit. However, no significant difference was detected in cognitive or nonmotor symptoms in this trial. Therefore, the authors resolved to separately analyze the effects on nonmotor symptoms by different subdomains (Athauda et al., 2018). They reported that exenatide had improvements in mood, and regarding cognition, they observed a trend with a 3.7 times (95% CI: 27.0–0.51; P = 0.198) inferior likelihood at 48 weeks of suffering mild cognitive impairment compared to placebo.

Later, the same group published a *post hoc* analysis describing that patients with lower MDS-UPDRS-2 scores and tremor-dominant phenotype had the best response to exenatide, while patients over 65 years old and older age of onset showed the worst response (Athauda et al., 2019b). However, the duration of disease also influenced the results of treatment response to nonmotor symptoms, given that the effects were more important in patients with a duration of disease under 4 years. Interestingly, the weaker improvement in cognition was in the tremor-dominant phenotype, while there was a positive

trend in obese patients or those with insulin resistance (all patients included were nondiabetic). This encouraged a study to assess the activity of Akt and brain insulin with biomarkers for neuron-derived exosomes (Athauda et al., 2019a). The exenatide-treated group had an increase in IRS1 phosphorylation and Akt and mTOR expression, and total mTOR and phosphorylated mTOR were associated with better motor scores. However, an important limitation of these studies is the lack of information regarding sex and the low rate of females included in the studies, given the possible susceptibility of females to the higher vulnerability of diabetic women to PD.

In 2020, two meta-analyses were published evaluating the effects of exenatide in PD in human trials. Wang et al. (2020) concluded that exenatide administration is associated with benefits at 12 months on motor and cognitive scales, nonmotor problems, and even on the UPDRS IV scale. The Cochrane study (Mulvaney et al., 2020) observed low evidence of motor benefits (mean difference of –3.1; 95% CI: –6.11 to –0.09), especially when adjusting results for baseline severity, but with uncertain results in nonmotor or cognitive symptoms.

Based on the current results, other trials are being conducted to evaluate the effect of exenatide in PD, such as the phase 3 exenatide-PD3 trial (NCT04232969) (including 200 patients over 2 years) or the phase 1 EudraCT 2019–000732-26 trial (NCT03456687). Moreover, a phase 2 study testing NLY01 (a pegylated form of exenatide) in early untreated PD patients (NCT04154072) and an extended release Ex4 formulation (PT320) is under a phase 2a trial in early PD patients (NCT04269642).

In addition to exenatide, other GLP1RAs are being studied in human clinical trials, such as liraglutide (NCT02953665, phase 2, randomized, double-blinded, placebo-controlled trial measuring nonmotor symptoms and motor changes after 14 months), semaglutide (NCT03659682, placebo-controlled, double-blind, 2-year trial with 270 early PD) or lixisenatide (NCT03439943, multicenter parallel groups, 2-arm, randomized, placebo-controlled, double-blind, proof-of-concept phase II French trial with early PD subjects).

DDP4 inhibitors

DDP4 inhibitors restrain peripheral GLP1 degradation, but they poorly cross the BBB (except omaglitpin), so their action occurs by increasing GLP1 levels. Some positive results have been published in animal models with Vildaglitpin (Abdelsalam and Safar, 2015), Saxagliptin (Nassar et al., 2015), Linaglitptin (Kabel et al., 2018) and Sitaglitpin (Badawi et al., 2019), but the doses used in these studies were higher than those administered in humans, so extrapolating the results is difficult.

Regarding data in humans, the incidence of PD significantly decreased in individuals receiving DDP4 inhibitors, as reported in case-control studies (Svenningsson et al., 2016) (including villagliptin, sitaglipin and saxagliptin) (OR = 0.23; 95% CI: 0.07–0.74) and longitudinal cohort studies (incidence rate ratio 0.64; 95% CI: 0.43–0.88; $P < 0.01$) (Brauer et al., 2020). A recent retrospective study observed a beneficial effect of DDP4 inhibitors in diabetic PD patients, who showed higher baseline dopamine transporter availability and better motor performance than nondiabetic patients or diabetic patients who did not receive DDP4 inhibitors (Jeong et al., 2021). However, the data in this study were retrospective, and the DDP4 group was small.

GIP receptor agonists

GIP (also known as glucose-dependent insulin releasing polypeptide) is secreted after food intake to induce insulin liberation. GIP receptors (GIPR) are extensively expressed in the brain, activating the MAPK, PI3K/Akt and cAMP/PKA pathways in both neurons and microglial cells. GIPR activation in microglia induces neurotrophic factors and restrains oxidative stress, diminishing apoptosis (Spielman et al., 2017). Agonists of GIPR have been reported to be more effective than GLP1RA in reducing neuroinflammation and the levels of α-synuclein in animal models (Li et al., 2017). Recently, dual GLP1R-GIPR agonists showed promising neuroprotective effects. Some of these had better results in experimental models when compared to Ex4 or liraglutide, such as DA3-CH or DA-CH5 (Yuan et al., 2017; Zhang et al., 2021).

Metformin

Metformin is able to cross the BBB and has an anti-inflammatory effect by reducing mitochondrial respiration dysfunction, decreasing MG and activating AMPK, which has prosurvival functions and decreases α-synuclein expression in animal models of PD. These beneficial effects have been observed in dopaminergic neurons (ameliorating apoptosis by MPTP) and in astrocytes (reducing their number and hypertrophy) in the substantia nigra and striatum, mainly by regulating protein phosphatase 2A activity and brain-derived neurotrophic factor expression (Katila et al., 2017). Moreover, Ryu et al. (2020) found that metformin can also control dyskinesia development and neuroprotection by stimulating brain-derived neurotrophic factors and the PI3K/Akt pathway. However, they reported that metformin did not affect dopaminergic cell death, but significant changes in microglial and astrocyte activation were demonstrated by regulating changes in astrocyte-specific genes (Ryu et al., 2020).

Nonetheless, other conflicting results have been published. A recent meta-analysis concluded that metformin did not show any effect on neurodegenerative diseases (OR = 1.04; 95% CI: 0.92–1.17) (Ping et al., 2020). Interestingly, a significantly increased PD incidence (OR = 1.66; 95% CI: 1.14–2.42) was noticed when compared with patients who did not take metformin. Although these results have to be interpreted with caution, they are especially relevant due to the frequent use of metformin worldwide, so further research is required to elucidate the interplay of metformin in neurodegeneration.

Thiazolidinediones

Thiazolidinediones (rosiglitazone, pioglitazone) bind to peroxisome proliferator-activated receptor gamma. Peroxisome proliferator-activated receptor-gamma was observed in the basal ganglia and can interfere, via PGC1α, with biogenesis of mitochondria and with inflammation pathways, reducing oxidative toxicity in several models. Thiazolidinediones have been demonstrated to ameliorate cell loss in dopaminergic neurons in MPTP mouse models, decrease inflammatory cytokines and promote changes in microglia to the M2 anti-inflammatory state (Pisanu et al., 2014). However, macaque models have raised the concern of possible impairment of levodopa's effects when dispensed together with pioglitazone, possibly due to pharmacologic interactions with L-dopa or with the nuclear retinoid X receptor (Huot et al., 2015).

Regarding human data, a significant decline in PD in diabetic patients taking thiazolidinediones was observed in a meta-analysis with retrospective studies (HR = 0.81; 95% CI: 0.70–0.93), particularly when the follow-up was longer than 5 years (HR = 0.74; 95% CI: 0.62–0.88) (Hussain et al., 2020). Another Taiwanese study reported that the combination with statins produced a further decline (Chang et al., 2020). However, none of these benefits was observed in prospective studies (Brauer et al., 2020) or human clinical trials (NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators, 2015), probably due to the low capability of pioglitazone to cross the BBB.

Conclusions

The pathophysiology of neurodegeneration in PD is heterogeneous and complex. Today, we must understand that we need to broaden our fight against the disease not just in the central nervous system but also targeting every possible measure that can slow neurodegeneration as early as possible. Epidemiological evidence and experimental data support the interaction between PD and DM, and both conditions are increasingly prevalent worldwide, being both especially associated with aging. As we have previously seen, treatments for DM show promising neuroprotective results in PD patients, including diabetic and non-DM patients, independent of glycemic control. Therefore, the possible role of antidiabetic treatments against PD is an encouraging field to repurpose antidiabetic drugs as neuroprotective treatments. Side effects of GLP1RA, such as weight loss and gastrointestinal symptoms, might be a limitation for PD patients, and further studies with larger populations and longer follow-up periods are needed. However, there is enough evidence to underline the importance of glycemic control in patients with PD to reduce the effect of glucotoxicity and to encourage further clinical trials with antidiabetics in PD.

PD should be considered a systemic disease rather than just as a neurodegenerative disorder, as nonneurologic processes such as DM can determine the development and aggravate the severity of the neurodegenerative process. Moreover, this can facilitate new measures to fight PD but also enable us to identify high-risk subjects for developing PD and therefore provide timely neuroprotective treatments.

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