

# Diabetes mellitus and Parkinson's disease: dangerous liaisons between insulin and dopamine

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## Abstract

The relationship between diabetes mellitus and Parkinson's disease has been described in several epidemiological studies over the 1960s to date. Molecular studies have shown the possible functional link between insulin and dopamine, as there is strong evidence demonstrating the action of dopamine in pancreatic islets, as well as the insulin effects on feeding and cognition through central nervous system mechanism, largely independent of glucose utilization. Therapies used for the treatment of type 2 diabetes mellitus appear to be promising candidates for symptomatic and/or disease-modifying action in neurodegenerative diseases including Parkinson's disease, while an old dopamine agonist, bromocriptine, has been repositioned for the type 2 diabetes mellitus treatment. This review will aim at reappraising the different studies that have highlighted the dangerous liaisons between diabetes mellitus and Parkinson's disease.

**Key Words:** dopamine; GLP-1; insulin; Parkinson's disease; type 2 diabetes mellitus

## Introduction

The relationship between type 2 diabetes mellitus (T2DM) and Parkinson's disease (PD) has been already demonstrated over the '60s, disclosing a significantly high prevalence of T2DM in parkinsonian patients (Sandyk, 1993). These initial epidemiological studies opened the field to further experimental works, investigating the possible functional link between insulin and dopamine (DA). Evidence for the presence of biogenic amines in the mammalian endocrine pancreas was originally reported by Falck and Hellman (1963), while functional studies supported a possible role of intracellular  $\beta$  cell monoamines in the regulation of insulin secretion (Wilson et al., 1974; Ericson et al., 1977). Subsequently, the development of molecular biology allows us to identify entire functional DA signaling machinery in pancreatic  $\beta$ -cells (Rubi et al., 2005; Saisho et al., 2008). More recently, a role in insulin signaling has also been shown for  $\alpha$ -synuclein ( $\alpha$ -syn) and leucine-rich repeat kinase 2, proteins whose mutations are involved in the pathogenesis of PD (Gao et al., 2015; Funk et al., 2019). On the other hand, insulin receptors were localized throughout the brain (Unger et al., 1991; Schulingkamp et al., 2000), allowing the identification of the insulin signaling pathways. At present, there is no doubt about the presence of cerebral insulin and its action as a neuromodulator, even if it is still debated if insulin is brain-derived or produced outside the central nervous system (CNS) (Havrankova et al., 1979; Kleinridders et al., 2014; Zeng et al., 2016).

Key treatments for T2DM have been investigated in clinical trials for their possible neuroprotective effects in PD, opening a new field in the pharmacological research of this disease. At the same time, bromocriptine, a DA agonist treating PD, has been approved by the United States Food and Drug Administration (FDA) for T2DM therapy. Here, we will review

the studies that have traced a red thread through glucose metabolism and neurodegenerative diseases, specifically addressing the link between T2DM and PD.

## Literature Search Strategy and Selection Criteria

The articles included in this review were retrieved by an electronic search of the PubMed database from inception to September 30, 2020 for literature describing epidemiological, experimental, and therapeutic studies on this topic. Searches were conducted using the following key words: insulin and dopamine, glucose and Parkinson's disease, diabetes and neurodegeneration. Articles were included if they were deemed to contribute to the understanding of the possible functional link between insulin and dopamine.

## Epidemiological Studies

### Is T2DM a predisposing factor for PD?

The analysis of the initial epidemiological studies, concerning the association between T2DM and PD, led Sandyk to assert there is a wide agreement that PD is associated with a significant prevalence of diabetes mellitus (Sandyk, 1993).

The main question emerging from this analysis was related to the impact of hyperglycemia on the motor symptoms of PD, a matter still debated today. Subsequent epidemiological investigations, based on the strong biological evidence emerging from functional and molecular studies, have analyzed larger cohorts of patients aiming to evaluate a real connection between PD and T2DM.

T2DM as a risk factor of developing PD has been confirmed in different ethnic groups (Hu et al., 2007; Schernhammer et al., 2011; Bosco et al., 2012; Sun et al., 2012; Yue et al., 2016; Yang et al., 2017; De Pablo-Fernandez et al., 2018), and PD patients resulted to be insulin-resistant (Bosco et al., 2012).

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## Review

Other investigations emphasized the role of comorbid diabetes in impairing motor and/or cognitive domains (Cereda et al., 2012; Kotagal et al., 2013), and the data were confirmed by imaging studies (Ong et al., 2017; Chung et al., 2018; **Table 1**).

Conversely, these data were not confirmed by other authors who found no association at all (Palacios et al., 2011; Savica et al., 2012) or even inverse association (Driver et al., 2008; D'Amelio et al., 2009; Miyake et al., 2010; Cereda et al., 2011; Lu et al., 2014; **Table 2**). Those inconsistent results may be due to study heterogeneity (case-control vs. cohort), the definition of PD (direct examination vs. self-report), the definition of T2DM (formal glucose/insulin measurement, medical records, or self-report), and disease duration since the diagnosis of T2DM.

Interestingly, multi-center analysis of T2DM patients with and without PD compared many diabetes endpoints. T2DM patients with PD showed a better metabolic control, probably due to more rigorous follow-ups (Scheuing et al., 2013).

Despite these conflicting results, in the last decade, there has been a rapidly increasing interest in investigating the connection between T2DM and PD, leading to the hypothesis that new drugs for diabetes mellitus might alter the natural history of PD itself. Furthermore, a new formulation of bromocriptine, an old antiparkinsonian drug, has been specifically approved by the FDA for the treatment of T2DM.

## Functional Studies

### DA in the endocrine pancreas

Several *in vitro* studies and preclinical investigations on animal models have confirmed the seminal histochemical and histological reports of Falck and Hellman (1963). These scientists demonstrated, by using the formaldehyde-induced fluorescence method, the intracellular presence of catecholamines in pancreatic islets of different mammalian species, in which adrenergic and cholinergic fibers were identified (Lakomy and Chodkowska, 1984). The pancreatic beta cells appear to work such as the neurons, as they were able to decarboxylate L-DOPA to DA, as observed in experimental animals (Cegrell, 1968).

The main question derived from these experimental observations concerned the role and the mechanism underlying dopaminergic transmission in the endocrine pancreas. In the first instance, the *in vitro* effects of adrenergic and cholinergic drugs on pancreatic tissues, observed by Malaisse et al. (1967) showed the insulin secretion to be stimulated by acetylcholine and  $\beta$ -adrenergic receptors, and inhibited by  $\alpha$ -adrenergic receptors. Possible roles of intracellular  $\beta$  cells monoamines in regulating insulin secretion have been subsequently provided from *in vitro* and *in vivo* experiments (Feldman et al., 1970; Wilson et al., 1974). The presence of DA in secretory granules of the pancreatic  $\beta$ -cells

**Table 1 | Epidemiological studies supporting the association between T2DM and PD**

Study	Study design	Main results
Hu et al., 2007	Prospective, cohort study, Finnish population	T2DM associated with an elevated risk of PD in both sex
Schernhamer et al., 2011	Case-control, Danish population	T2DM is associated with an increased risk of PD, especially younger onset PD
Bosco et al., 2012	Case-control, Italian population	Insulin resistance is significantly higher in PD patients with dementia than PD patients without dementia
Cereda et al., 2012	Retrospective, case-control	T2DM onset before PD onset is a risk factor for more severe PD symptoms
Sun et al., 2012	Retrospective, cohort study, Chinese population	T2DM is associated with an increased risk of PD onset, stronger in women and younger patients
Kotagal et al., 2013	Case-control	PD patients with T2DM displayed greater postural instability and gait difficulty
Bohnen et al., 2014	Case-control	T2DM is associated with more severe cognitive impairment in PD
Yue et al., 2016	Cohort study meta-analysis	T2DM is associated with an increased 38% PD risk
De Pablo-Fernandez et al., 2017	Cross-sectional study, Spanish population	The risk of PD in T2DM might be limited to longer disease duration
Ong et al., 2017	Prospective	Longitudinally T2DM in PD results in a greater rate of cognitive decline with higher white matter atrophy
Yang et al., 2017	Retrospective, case-control, Chinese population	T2DM increases the risk of PD. The magnitude of association is higher in women
Chung et al., 2018	Inter-group comparative analysis	Coexistent T2DM in PD patients may have a detrimental effect on the baseline striatal dopamine loss, and cognitive performance
De Pablo-Fernandez et al., 2018	Retrospective, cohort study	Increased rate of subsequent PD in T2DM patients
Pagano et al., 2018	Cross-sectional	T2DM may predispose toward a PD-like pathology. T2DM present in PD patients can induce a more aggressive phenotype

PD: Parkinson's disease; T2DM: type 2 diabetes mellitus.

**Table 2 | Epidemiological studies against the association between T2DM and PD**

Study	Study design	Main results
Driver et al., 2008	Prospective, cohort study, US population	T2DM is associated with an increased risk of PD, but it is not a preceding risk factor of PD
D'Amelio et al., 2009	Case-control	T2DM consistently lower among PD cases compared to controls
Miyake et al., 2010	Case-control	Inverse associations of hypertension, hypercholesterolemia, and diabetes mellitus with the risk of PD in Japan
Cereda et al., 2011	Meta-analysis	No conclusive evidence of the association between T2DM and PD
Palacios et al., 2011	Prospective	No evidence between baseline T2DM and PD
Xu et al., 2011	Prospective, cohort study, US population	T2DM in older patients is associated with a modest increase in PD
Savica et al., 2012	Case-control	No association between T2DM and later development of PD
Lu et al., 2014	Case-control meta-analysis	T2DM patients may have a decreased incidence of PD

PD: Parkinson's disease; T2DM: type 2 diabetes mellitus.

was later confirmed by electron microscopy (Ericson et al., 1977). This histological localization, according to the authors, demonstrated that hyperglycemic effects might have been driven by DA through insulin storage or releasing mechanism.

Currently, this hypothesis has been validated by molecular studies that highlighted the mechanisms of DA stimulation on the endocrine pancreas. The whole DA secretion mechanisms and signaling machinery of pancreatic  $\beta$  cells have been better characterized. Tyrosine hydroxylase, the rate-limiting enzyme in DA biosynthesis, converting L-DOPA in DA and specific marker for catecholamine-synthesizing cells, was identified in  $\beta$ -cells. Moreover, electron microscopy studies showed how the enzyme monoamine oxidase (MAO), involved in the deamination of catecholamines, is co-localized along with insulin in secretory granules of  $\beta$ -cells. Vesicular monoamine type 1 (VMAT-1) and type 2 (VMAT-2) transporters, essential for the vesicular storage of DA, were respectively identified in rat and human pancreas (Mezey et al., 1996; Anlauf et al., 2003). DA transporter (DAT), a plasma membrane protein, which transports released DA back into the cell or may also function in reverse mode releasing DA, was found in exocrine and endocrine pancreatic cells (Mezey et al., 1996). DA receptors, classified as D1-like (D1 and D5) and D2-like receptors (D2, D3, and D4), possible mediators of the DA action on the insulin secretion, are expressed in  $\beta$ -cells (Rubi et al., 2005; Bini et al., 2020).

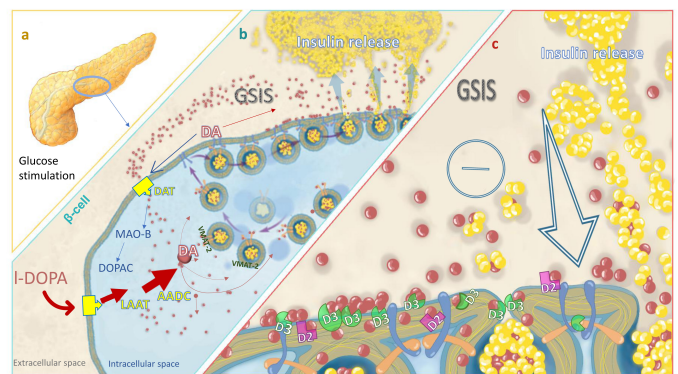
The demonstrated presence of the DA machinery leaves unsolved the following problems: a) From where the DA comes in the endocrine pancreas? b) How that machinery works on insulin secretion?

Here are two possible explanations: a) The presence of DA in the pancreas seems to exclude a neuronal production. The existence of a peripheral DA system independent of the sympathoadrenal system was first suggested by the detection of a considerable DA concentration in the body not metabolized to other catecholamines (Mezey et al., 1996).

Eisenhofer et al. (1997) inferred a production of DA by mesenteric organs because the higher concentrations of DA and metabolites were found in portal venous than arterial plasm. They introduced the concept of a “third catecholamine system” in which the DA, synthesized from decarboxylation of L-DOPA in nonneuronal cells, would act locally as an autocrine/paracrine effector and undergo inactivation by sulfconjugation before entering the bloodstream (Goldstein et al., 1999). Clinical studies evaluating the plasma concentrations of DA sulfate after fasting and food intake showed increased DA sulfate and L-DOPA, after meal ingestion, but normal concentrations after fasting and L-DOPA infusion, in patients with peripheral autonomic failure and patients undergoing gastrointestinal surgery, compared with healthy subjects. In patients deficient of L-aromatic amino acid decarboxylase (L-AADC), the L-DOPA converting enzyme in DA, they registered very low concentrations of DA sulfate in the same conditions (Goldestein et al., 1999, 2003).

Despite the robust evidence of the presence of DA, strengthened by *in vitro* and *in vivo* studies (Mezey et al., 1996; Simpson et al., 2012; Ustione and Piston, 2012), the identification of an endogenous synthesis of DA in  $\beta$ -cells, is still a complex work. Farino et al. (2020) investigated the possible mechanism underlying metabolic disturbances induced by the antipsychotic drug and argued a DA production and secretion by  $\beta$ -cells when provided DA precursors, such as L-DOPA deriving from protein and carbohydrate meals. This release would be regulated by glucose stimulation (Farino et al., 2020). Lastly,  $\beta$ -cells appear to be able to de novo synthesize DA in two kinds of mouse strains (Mitok et al., 2018).

b) The role of DA in insulin secretion seems to be inhibitory,



**Figure 1 | A schematic overview of the possible inhibitory role of DA in the pancreas.**

(a) Glucose stimulation increases L-DOPA uptake, forming intracellular DA in  $\beta$ -cells. (b) VMAT-2 transports cytoplasmic DA into insulin-containing vesicles. On GSIS, insulin and DA are delivered to the extracellular space. (c) DA diffuses to neighboring  $\beta$ -cells and binds to D2R and/or D3R, inhibiting further insulin secretion. By DAT, DA is recycled and degraded by MAO-B. AADC: Amino acid decarboxylase; D2: dopamine receptor 2; D3: dopamine receptor 3; DA: dopamine; DAT: dopamine transporter; DOPAC: 3,4-dihydroxyphenylacetic acid; GSIS: glucose-stimulated insulin secretion; L-DOPA: L-3-4-dihydroxyphenylalanine; LAAT: L-type amino acid transporter; MAO-B: monoamine oxidase-B; VMT-2: vesicular monoamine transporter 2.

modulated by DA signaling machinery. The insulin granules express D2 receptors (D2R) and, during insulin secretion glucose-stimulated (GSIS), DA and insulin appear delivered to the cell surface, where D2R binds to DA, inhibiting the GSIS insulin secretion (Rubi et al., 2005; Simpson et al., 2012). Other scholars localized D2R on the  $\beta$ -cell plasma membrane but showed D3Rs to be involved in  $\beta$ -cell DA signaling (Ustione and Piston 2012; Farino et al., 2020; **Figure 1**).

A functional role of DAT and VMAT-2 has been hypothesized by the enhancement of insulin secretion after VMAT-2 and DAT inhibition (Ustione and Piston, 2012). The role of DA in modulating islet survival has also been demonstrated (Garcia-Barrado et al., 2015). In an imaging study, D2/D3 receptor agonist radioligand 11C-(1)-4-propyl-9-hydroxynaphthoxazine (PHNO) was identified as a tracer to measure  $\beta$ -cell mass (Bini et al., 2018). The same radioligand has been subsequently used to evaluate residual  $\beta$ -cell mass in type 1 diabetes mellitus (T1DM) and, in the same study, by using immunohistochemistry, it was demonstrated a lack of staining for the D2R, DA D3 receptor (D3R), and insulin in a T1DM pancreatic tissue, whereas D2R, D3R, and insulin were colocalized in the pancreas of healthy controls (Bini et al., 2020).

### Insulin in the brain

If the DA in the gut appears to act as a metabolic regulator, the insulin in the brain shows a neuromodulatory action through the insulin signaling pathways. Different studies have shown the reciprocal regulation that insulin and DA can exert each other.

Intracerebral insulin comes from pancreatic  $\beta$ -cells, crossing the blood-brain barrier via a saturable transport process (Havrankova et al., 1978). Neuronal *de novo* synthesis of insulin was also demonstrated in primary cultures from rat brains (Clarke et al., 1986). Molecular studies, performed in experimental animals, identified insulin transcripts in specific brain regions, as pyramidal cells of the hippocampus, dentate gyrus, prefrontal cortex, entorhinal cortex, thalamus, and granular cell layer of the olfactory bulbs (Schechter et al., 1988; Devaskar et al., 1994; Kuwabara et al., 2011). Insulin mRNA has been shown to be strongly expressed in GABAergic neurogliaform cells in the cerebral cortex, which showed

insulin-like effects according to the detection of excitatory postsynaptic currents (Molnár et al., 2014). Insulin protein expression was detected in rat astrocytes, as well, where appeared to recover neuronal activity after hypoglycemia, in synergistic action with insulin growth factor-1 (Fernandez, 2017), and to exert neuroprotective effects (Pitt et al., 2017; Takano et al., 2018). The uneven distribution through the brain of insulin signaling machinery should give the reason for the different actions that insulin plays in the CNS, beyond the glucose metabolism regulation. The brain insulin receptors (IRs) have been identified in neurons and astrocytes from human cerebral cortex, rat olfactory bulb, hypothalamus, hippocampus, and cerebellum (Havrankova et al., 1978; Unger et al., 1991; Shulingkamp et al., 2000), DA neurons of the ventral tegmental area (VTA) and substantia nigra (SN) (Figlewicz et al., 2003). Among the glucose transporters, distributed through the brain (Mc Ewen and Reagan, 2004), insulin regulates glucose transporter 4 (GLUT4) and glucose transporter 8 (GLUT8), localized in neuronal cell bodies in cortex, cerebellum, hypothalamus, hippocampus, and amygdala (Jurcovicova et al., 2014)

Binding to its specific receptors and through the consequent tyrosine phosphorylation of insulin receptor substrate (IRS) docking proteins, insulin can trigger two main downstream pathways: the phosphoinositide-3-kinase (PI3K/Akt) cascade, involved in neuronal survival, and the Ras-Raf-mitogen-activated protein kinase (MAPK/ERK) signaling, involved in cell death (White and Kahn, 1994). Alternatively, through the SHC/ERK1/2 pathway, insulin promotes neuronal survival and plasticity (van der Heide et al., 2006), improving neuronal antioxidant defense and protecting against neuronal apoptosis (Duarte et al., 2008).

### Insulin in brain reward circuitry

The important relationship between insulin and DA emerges even more in the brain reward system, involving the mesolimbic DA pathway (Ikemoto, 2007). DA plays a central role in food reward, energizing feeding, and reinforcing food-seeking behavior (Morton, 2006; Wise, 2006) and substantial body of evidence showed that insulin modulates the reward circuitry. In dopaminergic neurons located in VTA and substantia nigra pars compacta (SNpc), the IRs are coexpressed with TH (Figlewicz et al., 2006). The inactivation of the IRs signaling in mouse TH-expressing cells resulted in a hyperphagic phenotype, increased body weight, and fat mass (Konner et al., 2011). In previous studies, it was observed by using intracerebroventricular administration of insulin (icv), the synergistic action of this hormone when paired with D2R antagonism in reducing sucrose consumption (Sipols et al., 2000). Increasing mRNA levels for the DAT, responsible for the DA reuptake have been detected in VTA and SNpc of rats chronically treated with icv insulin infusion and in hyperinsulinemic obese rats. Thus, insulin appeared to decrease DA concentration in VTA via increased reuptake of DA through DAT, reducing conditioned place preference to high-fat food and modulating the reward-related feeding behavior (Figlewicz et al., 2006). Moreover, an insulin-mediated decrease of DA in VTA suppressed the salience of food once satiety had reached (Mebel et al., 2012). Insulin as a reward signal has been well demonstrated by Stouffer et al. (2015). They observed an increased release of DA in nucleus accumbens (Nac) and caudate-putamen (Cpu) stimulated by insulin through striatal cholinergic interneurons expressing IRs, in food-restricted rats but not in obesogenic rats. According to the authors (Stouffer et al., 2015), such striatal insulin signaling enhances DA release to influence food choice.

Evidence of the insulin action in the human brain comes from neuroimaging studies mirroring molecular studies. Former studies applying auditory evoked brain potentials (AEP) and behavioral tests, after insulin infusion, suggested a direct

influence of the hormone in improving cognitive functions in human subjects (Kern et al., 2001). Such increased neuronal activity was specifically localized in the medial temporal lobe, including the hippocampus, by functional magnetic resonance imaging (Rotte et al., 2005).

Studies of insulin in the human brain rely on intranasal administration. Via this delivery, insulin rapidly reaches the CNS through the olfactory nerve and it is possible to evaluate its direct effects within the brain, overcoming systemic effects on peripherally blood glucose or insulin levels (Kern et al. 1999; Born et al., 2002). Insulin appears as a metabolic key signal in the homeostatic mediation of satiety as resulted from the comparison between the effect of intranasal insulin administration and placebo on the brain of subjects processing food pictures analyzed by fMRI (Guthoff et al., 2010).

As also observed in experimental animals (Szczycka et al., 2001), intranasal insulin action in the human brain regulates the peripheral insulin sensitivity in a time-dependent manner, fitting with insulin kinetics after a meal (Heni et al., 2012). Moreover, Heni et al. (2014) investigated the eating behavior in response to food cues and demonstrated an enhanced activity of the putamen after glucose ingestion, without difference from water ingestion in overweight subjects, contrary to lean people that showed different activity patterns to low caloric and high caloric stimuli.

### Insulin in the Pathophysiology of Parkinson's Disease

The emerging role of insulin as a neuromodulator appears a possible puzzle piece contributing to the neurodegeneration pathway of PD. The etiology of PD remains unknown despite genetic and environmental factors, affecting fundamental cellular processes, have been identified and correlated to the specific neurodegenerative process of PD. One of these is oxidative stress, intimately linked to other components of the degenerative process, such as mitochondrial dysfunction, excitotoxicity, nitric oxide toxicity, and inflammation, even if it is still difficult to determine whether oxidative stress leads to, or is a consequence of these events (Kalia and Lang, 2015).

Ramalingam and Kim demonstrated that insulin reduces the hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>)-induced oxidative damage in neuronal and glial cells (Ramalingam and Kim 2014, 2016a). The same authors observed the neuroprotective action of insulin in cell cultures treated with 1-methyl-4-phenyl pyridinium (MPP<sup>+</sup>), a neurotoxin derived from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which causes oxidative stress, mitochondrial dysfunction, and ultimately apoptotic cell death *in vitro*. In this case, pretreatment of insulin prevented cell death and lowered nitric oxide (NO) release, reactive oxygen species (ROS), and calcium (Ca<sup>2+</sup>) influx induced by MPP<sup>+</sup> (Ramalingam and Kim, 2016b). The neuroprotective effects of insulin were confirmed in the 6-hydroxydopamine (6-OHDA)-based rat PD model. Treatment with intranasal insulin significantly ameliorated 6-OHDA-induced motor impairments, providing potent protection of DA neurons in the SNpc against 6-OHDA neurotoxicity (Pang et al., 2016).

Such actions of insulin are ascribed to the suppression of the glycogen-synthase kinase3 (GSK-3) activity, a crucial multi-target kinase, whose dysregulation is implicated in PD pathogenesis and promotion of Lewy bodies formation, the neuronal inclusions representing the pathological hallmark of PD (van der Heide et al., 2006; Albeley et al., 2018)

The insulin signaling pathway embraces two proteins, whose mutations are closely involved in the pathogenesis of PD: alpha-synuclein ( $\alpha$ -syn) (Polymeropoulos et al., 1997) and

Leucine-Rich Repeat Kinase 2 (LRRK2) (Paisàn-Ruiz et al., 2004). The physiological roles of  $\alpha$ -syn, which is the main component of Lewy bodies and Lewy neurites in the PD brain, are not completely clear, ranging from chaperone activity to management of synaptic vesicle trafficking (Bendor et al., 2013). Expressed in presynaptic sites in the CNS,  $\alpha$ -syn was found to be present also in several non-neuronal tissues (Askanas et al., 2000; Baltic et al., 2004; Barbour et al., 2008), and its possible spreading through different organs in PD has determined an unsolved discussion among the researchers (Braak et al., 2003; Olanow and Prusiner 2009; Bendor et al., 2013).

Alpha-syn has also been identified in the pancreas (Ueda et al., 1994) and successively localized on the insulin-secretory granule interacting with the  $K^+$ ATP channel. This protein has been shown to functionally act as a brake on insulin secretion; thus in diabetes, when  $\alpha$ -syn interaction with secretory granules becomes excessive, it should be able to compromise insulin secretion (Geng et al., 2011). Alpha-syn overexpression appears to negatively regulate the insulin receptor substrate-1 (IRS-1), impairing the PI3/Akt insulin signaling via mTORC1/S6K1 activation and promoting insulin resistance (Gao et al., 2015). On the other hand, it has been observed that the acute administration of  $\alpha$ -syn in experimental animals promotes glucose metabolism in adipose tissue and skeletal muscle, through GAB1/PI3K/AKT transduction pathway (Rodriguez-Arujo et al., 2013). Metabolic changes were detected in  $\alpha$ -syn A53T mutant mouse model of PD, as they are resistant to both high fat-induced obesity and high fat diet-induced insulin resistance (Rothmann et al., 2013). In a study analyzing the serum of 1152 subjects from medical check-ups, low plasma levels of  $\alpha$ -syn were associated with insulin resistance, as serum  $\alpha$ -syn levels were inversely correlated with insulin resistance indicator such as homeostatic model assessment for insulin resistance (HOMA-IR). In the same study,  $\alpha$ -syn deficient mice displayed alterations in glucose and insulin response during diet-induced insulin resistance. Moreover, the measurement of insulin sensitivity by hyperinsulinemic-euglycemic clamp assessment in  $\alpha$ -syn knockout mice fed with a high-fat diet has shown severe insulin resistance in adipose tissue and skeletal muscle (Rodriguez-Arujo et al., 2015).

Conversely, it has been demonstrated action on  $\alpha$ -syn from molecules structurally very close to insulin, the insulin-like growth factor 1 (IGF-1), which, together with insulin and IGF-2, is referred to insulin-like peptides (ILPs), belonging to the insulin superfamily of peptides (Fernandez and Torres-Alemán, 2012) and the insulin-degrading enzyme (IDE) (Duckworth et al., 1998). IGF-1 is a potent growth factor in the CNS (Dyer et al., 2016), and its protective effects against loss of dopaminergic neurons have been proved in cell culture and animal model of PD studies (Offen et al., 2001). The IGF-1 receptor (IGF-1R) and the IR can form functional hybrids with similar affinities for IGF1 and insulin, indicative of cooperation between these two ILPs. IGF-1 signaling, like insulin, can proceed through the RAS-ERK and PI3K/Akt cascades. Through the activation of PI3K/Akt pathways, IGF-1 rescued  $\alpha$ -synuclein toxicity and suppressed  $\alpha$ -syn aggregation (Chung et al., 2011). Higher IGF-1 serum levels were found in newly diagnosed untreated PD patients comparing to healthy controls, providing evidence for IGF-1 as a possible biomarker for early PD. Given the neuroprotective action of IGF-1, it has also been hypothesized that increased serum IGF-1 levels in early PD may reflect a compensatory effort to protect dopaminergic neurons from neurodegeneration (Godau et al., 2010, 2011). Moreover, Picillo and co-workers demonstrated a significant correlation between IGF-1 serum levels and progression of motor symptoms in a cohort of early, drug-naïve PD patients, in whom higher IGF-1 levels matched with a higher dopaminergic score (Picillo et al., 2013).

The IDE, a zinc metalloprotease, so named by its degradation

action on receptor bound-insulin, has multiple cellular functions including binding and regulatory functions. Insulin degradation is tightly linked to insulin action and it has been suggested that intracellular interactions of insulin-degrading enzyme (IDE) may be involved in insulin control of cellular protein degradation and fat oxidation (Duckworth et al., 1998). Intriguingly, IDE *in vitro* prevented the formation of  $\alpha$ -syn pathogenic amyloid fibrils in a mutual interaction considering that the binding of  $\alpha$ -syn to IDE enhanced the proteolytic activity of IDE (Sharma et al., 2015).

A role in insulin signaling on LRRK2, a crucial protein in the synaptic vesicle recycling regulation (Maas et al., 2017) and DA receptor trafficking (Rassu et al., 2017), has been shown in LRRK2 deficient cells from experimental animals and fibroblasts of PD patients with G2019S mutated-LRRK2. The insulin-induced translocation of GLUT 4 containing vesicles to the cell surface appeared to fail in LRRK2 deficiency, highlighting an essential role of LRRK2 in the phosphorylation of Rab10, a RabGTPase required in the PI3/Akt signaling pathway for the insulin-induced translocation of GLUT 4 (Funk et al., 2019).

## Dysregulated Pathways in Type 2 Diabetes Mellitus and Parkinson's Disease

Experimental pieces of evidence show pathways intersecting between T2DM and PD (Santiago and Potashkin, 2013). Hyperglycemia in diabetes appears to be the unifying mechanism inducing dysregulation of pathways essential for cell life (Bronwlee, 2001). Excess of the intracellular glucose saturates the polyol pathway, lowering the reduced form of glutathione (GSH) and consequently increasing the cell susceptibility to oxidative stress. Increased oxidative stress, due to overproduction of reactive species of oxygen (ROS) in dopaminergic neurons, with a low level of GSH, is also described as a possible mechanism of neurodegeneration in the pathogenesis of PD (Lang and Lozano, 1999). Hyperglycemia causes mitochondrial superoxide overproduction with an increased formation of advanced glycation end products (AGEs), modifying circulating proteins that, bound to AGE receptors, trigger the production of inflammatory cytokines (Bronwlee, 2005; Giacco and Bronwlee, 2010). Neuroinflammation is involved in the neurodegeneration pathways (Kalia and Lang, 2015) and glycation is considered an unavoidable age-associated process that might play a role in PD. The levels of AGEs were found to be increased in the brains of patients suffering from synucleinopathy (Dalfo et al., 2005) and glycation of  $\alpha$ -syn enhanced its toxicity, *in vitro* and *in vivo*, in *Drosophila* and mice (Miranda et al., 2017). Moreover, methylglyoxal, a highly reactive glycation agent was described to show chemical similarity with DA oxidation products, highly toxic for dopaminergic neurons when they are not physiologically removed (Biosa et al., 2018). The formation of toxic aggregates of the islet amyloid polypeptide (IAPP) in diabetes has been observed to contribute to the  $\beta$ -cell dysfunction, thus T2DM can be included in the group of protein misfolding disorders, together with PD and other neurodegenerative diseases. Such as in PD, also in T2DM the alterations of the autophagy, the major clearance mechanism for lysosomal degradation of damaged proteins, lead to the accumulation of protein aggregates which results in cytotoxicity (Mukherjee et al., 2016).

## Antidiabetic Drugs in Parkinson's Disease

### Tolbutamide

Already back in 1960, Gates and Hyman (1960) reported an open-label treatment of 15 parkinsonian patients with tolbutamide, a drug belonging to the sulfonyleurea class of insulin secretagogues, which act by stimulating pancreatic

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cells to release insulin. This compound was able to markedly improve tremor and rigidity in 12 of the patients. A similar study, with analogous conclusions, was reported by Barbeau et al. (1961).

### Glitazones

More recently, different studies analyzed the effects of glitazones (GTZ) on PD pathology, targeting the inflammatory process presumably involved in neurodegeneration. GTZ are synthetic ligands of the thiazolidinedione class, used as antidiabetic agents by their insulin-sensitizing effects, decreasing insulin resistance and hyperglycemia (Nolan et al., 1994). Such drugs are agonists of peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), a member of the nuclear receptor superfamily that regulates carbohydrate and lipid metabolism (Delerive et al., 2001). In the brain, PPAR- $\gamma$  displays a regional distribution, high levels being expressed in the piriform cortex, olfactory tubercle, cerebellar cortex, microglia, astrocytes, oligodendrocytes, and neurons (Moreno et al., 2004; Cimini et al., 2005; Bernardo and Minghetti, 2008). In dopaminergic areas, co-localization with TH-positive neurons has been reported in the SNpc and the VTA (Sarruf et al., 2009; Carta et al., 2011). Although the issue of neuroinflammation as cause or consequence in PD pathophysiology remains controversial, an increasing amount of evidence strongly supports the active involvement of reactive microglia in the progression of neurodegeneration and suggests the possibility of targeting microglial response in the treatment of PD (Hirsch and Hunot, 2009; Long-Smith et al., 2009). *In vivo*, PPAR- $\gamma$  agonists have been shown to modulate inflammatory responses in the brain (Heneka et al., 2000). Neuroprotective effects were demonstrated in different animal models of PD, with different mechanisms in each of them. Barbiero et al. (2014) showed that pioglitazone prevented the degeneration of dopaminergic neurons in SNpc in the rat MPTP-model of PD and the decrease of DA levels in the striatum, protecting against hypolocomotion, depressive-like behavior, and memory impairment. The specific effect of pioglitazone on neuroinflammation was demonstrated in an animal model of PD (Pinto et al., 2016), in which dopaminergic neuron loss has been induced by a mitochondrial respiratory defect. In this case, L-DOPA treatment triggered atypical motor behavior, without preventing any neurodegeneration, but after the pioglitazone treatment, it was observed an improvement of motor symptoms, with a specific reduction of both microglial cell number in the midbrain and microglial activation in the midbrain and striatum. The action of pioglitazone on neuroinflammation was recently confirmed in a 6-OHDA animal model of PD, in which it was able to attenuate microglial activation, with increased survival of neurons in the hippocampus in rats with nigral lesions, along with a supposed antidepressant-like effect (Bonato et al., 2018).

Despite the numerous experimental pieces of evidence, similar pioglitazone effects were not replicated in PD patients. A clinical multi-center, double-blind, randomized trial assessed the pioglitazone effects in 210 participants with early PD, during 44 weeks of pioglitazone treatment associated with monoamine oxidase type B inhibitors. Pioglitazone did not demonstrate to slow the progression of motor impairment in early PD (NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators, 2015). Cohort studies also showed contradictory results concerning a supposed positive effect of pioglitazone on PD progression (Brauer et al., 2015; Connolly et al., 2015). Finally, a long-term retrospective study, performed on the Norwegian Prescription Database, analyzed the GTZ and metformin prescriptions during a 10-year period, to investigate the putative inverse association between GTZ use and PD occurrence. GTZ use was indeed associated with a decreased risk of developing PD, compared with metformin use in this nationwide study analyzing a T2DM population (Brakedal et al., 2017).

### Metformin

Metformin represents the first-choice oral drug for T2DM. It is a biguanide that improves insulin sensitivity with an increased skeletal myocyte glucose uptake and decreased hepatic glucose production (Bailey, 2017). In a large cohort study, the incident PD risk was analyzed in Taiwanese patients with T2DM taking metformin and/or the secretagogue sulfonylurea. Such an analysis confirmed T2DM as a risk factor for PD, which appeared doubled in the enrolled diabetic patients not taking oral antidiabetic agents, but that risk was significantly reduced in patients receiving metformin treatment. Sulfonylurea therapy increased PD risk, but this was reduced by the sulfonylureas association with metformin (Wahlqvist et al., 2012). A recent study on older adult United States veterans with T2DM evaluated the association between the length of metformin exposure and PD, showing that the risk reduction of this neurodegenerative disease seems to be associated with long-term metformin therapy (Shi et al., 2019). Speculating on the other possible mechanisms of action by metformin, this compound appears to activate proteins involved in mitochondrial function, restoring mitochondrial biogenesis and mitochondrial membrane potential, whose alterations are crucial elements of neurodegeneration in PD (Fitzgerald et al., 2017).

The more appealing function of metformin as a possible explanation of its neuroprotective role is its action on the gut hormone glucagon-like peptide 1 (GLP-1). Metformin sensitizes the cells to GLP-1 through PPAR- $\gamma$ , which increases the circulating levels of GLP-1 and, consequently, helps to control blood glucose (Mulherin et al., 2011).

### GLP-1 receptor agonists

GLP-1 is one of the two gut hormones, produced in the enteroendocrine cell of the small intestine that stimulates insulin secretion from the pancreas in response to food (Drucker, 2006; Muller et al., 2019). Named also incretin, by its capacity to potentiate insulin plasma levels after oral administration of glucose compared to intravenous glucose, its action is not restricted to the glucose homeostasis. GLP-1 was observed *in vitro* to enhance cell survival and inhibit apoptosis (Lovshin and Drucker, 2009). Such effects are mediated by binding to the GLP-1 receptor (GLP-1R), with the subsequent activation of PI3K, phosphorylating and activating different downstream signaling pathways. GLP-1Rs are expressed not only in pancreatic islet cells and peripheral tissues such as the heart, kidney, lungs but also in the frontal cortex, thalamus, hypothalamus, hippocampus, and substantia nigra (Alvarez et al., 2005), in both astrocytes and microglia, in which antioxidative and anti-apoptotic effects by treatment with GLP-1 were observed (Spielman et al., 2017). Turton et al. (1996) demonstrated the presence of an endogenous GLP-1 in the brain able to reduce food intake. The GLP-1R expression was investigated in the hippocampus, analyzing the possible action in learning and memory. It was found that mice lacking GLP-1R had learning deficits (During et al., 2003) and GLP-1 administration restored the spatial learning and memory performance, which were blocked by GLP-1 antagonist (Gault and Hölscher, 2008).

GLP-1R agonists are currently a common treatment for T2DM. Exenatide is the first GLP-1 analog approved by FDA, in 2005. It is a synthetic copy of the exendin-4 (Ex-4), the hormone found in the saliva of the venomous lizard Gila Monster (*Heloderma suspectum*), resistant to degradation by the circulating dipeptidyl peptidase IV (DPP-IV), which rapidly inactivates GLP-1 in humans. Ex-4 showed the feature of a neurotrophic factor inducing neurite outgrowth in *in vitro* model of neuronal differentiation and was able to rescue degenerating cells after NGF-mediated withdrawal (Perry et al., 2002).

A previous cell culture study demonstrated the protective effect of GLP-1 onto dopaminergic neurons against hypoxia and 6-OHDA-induced toxicity, while Ex-4 treatment elevated TH levels in those neurons. In the same study, Ex-4 prevented MPTP animal models of PD from neurodegeneration, showing improved motor function in mice (Li et al., 2009). The same protective action by GLP-1 was observed in the 6-OHDA rat animal model of PD (Jalewa et al., 2017). The compelling pieces of evidence of neuroprotective and neurotrophic actions of GLP-1 agonists led to initiate clinical trials on parkinsonian patients. An initial proof of concept with a single-blind trial design evaluated 45 patients with moderate PD who received subcutaneous exenatide injection for 12 months. The treatment resulted in significant and clinically relevant improvements in the motor and cognitive measures (Aviles-Olmos et al., 2013). A subsequent double-blind, placebo-controlled study from the same group confirmed the efficacy of this antidiabetic therapy in ameliorating motor symptom severity in PD patients (Athauda et al., 2014), opening an intense discussion about the development of this novel therapeutic strategy, also as a potential disease-modifying treatment (Simuni and Brundin, 2014; Athauda et al., 2017; Jankovic, 2017).

A *post hoc* analysis of the double-blind trial evaluating the exenatide effect was then performed to determine possible predictors of the motor response to exenatide. The possible changes in motor severity, non-motor symptoms, cognition, and quality of life after 48-week treatment with exenatide were evaluated among post-hoc subgroups defined by age, motor phenotype, disease duration, disease severity, body mass index, and insulin resistance. Results showed that patients with older age of onset and disease duration over 10 years responded less well to exenatide treatment, supporting the concept of recruiting patients at earlier disease stages in future clinical trials of GLP-1R agonists in PD (Athauda et al., 2019). Whether exenatide affects the underlying disease pathophysiology or simply induces long-lasting symptomatic effects remains uncertain. Clinical trials on the efficacy of liraglutide, a newer GLP-1 analogue, in PD are also ongoing. (ClinicalTrials.gov Identifier: NCT02953665) (Table 3).

## Antiparkinsonian Drugs in Type 2 Diabetes Mellitus

A controlled-release bromocriptine formulation (Cycloset), a DA D2 receptor agonist, has been approved by the FDA for

the treatment of T2DM in 2009. The action of bromocriptine in T2DM involves the enhancement of morning hypothalamic dopaminergic activity, resulting in improved insulin sensitivity and reduced plasma glucose, triglyceride, and free fatty acid levels.

The mechanism of bromocriptine action has been inferred from animal studies. Mammalian wild species change their metabolism according to the season, developing insulin resistance when food is scarce and surviving by increasing lipolytic activity, fat oxidation, hepatic glucose production, and gluconeogenesis to supply glucose in the CNS. Such insulin resistance reverts when the food becomes available again. The seasonal metabolic changes are regulated by endogenous dopaminergic and serotonergic action in SCN and ventromedial nucleus of hypothalamus (VMH), which plays a pivotal role in modulating autonomic nervous system function, hormonal secretion, peripheral glucose/lipid metabolism, and feeding behavior. DA levels are low during the insulin-resistant state and increase in the insulin-sensitive state (De Fronzo, 2011). Type 2 diabetic state appears to mimic the seasonal insulin-resistant state observed in mammals. Death of dopaminergic neurons in the CNS produces insulin resistance (Luo et al., 1997), and animal models of obesity show reduced DA levels in VMH and lateral hypothalamic nuclei (Oltmans, 1983). Systemic and intracerebral bromocriptine administration in insulin-resistant animals improved insulin sensitivity, reducing lipolysis and hepatic glucose production and gluconeogenesis (Luo et al., 1999). Type 2 diabetic individuals seem to have an early morning lowering of dopaminergic tone. Several human trials showed the efficacy of dopaminergic therapy, resulting in improved glycemic control above all in those subjects whose glycemia was poorly controlled by classic antidiabetic drugs such as metformin (Cincotta et al., 1996; Schwartz et al., 1996; Kamath et al., 1997). A just-released meta-analysis and sequential analysis of randomized clinical trials on the bromocriptine and cabergoline effects in T2DM patients showed reduced glycated hemoglobin (HbA1c), fasting plasma glucose, and triglycerides in diabetic patients without causing serious adverse effects (Andersen et al., 2021).

## Conclusion

A considerable amount of studies has analyzed the intersecting signaling pathways between DA and insulin, showing the role of the former as a metabolic regulator and the latter as a neuromodulator. Conflicting data come from

**Table 3 | Trials with antidiabetic drugs in PD**

Compound	Authors	Study design	Results
Glitazone	Brauer et al., 2015	Retrospective cohort study	Prescription of glitazone was associated with a lower incidence of PD
	NINDS Exploratory Trials in Parkinson's Disease (Net-PD) FS-ZONE Investigators, 2015	Phase 2, Multicentre, Double-Blind, Randomised Trial	Pioglitazone did not result to slow the motor impair progression in early PD
	Connolly et al., 2015	Cohort study	The use of glitazone might have a therapeutic benefit in slowing the progression of the disease
Metformin	Brakedal et al., 2017	Retrospective study	The use of glitazones is associated with a decreased risk of incident PD in populations with diabetes
	Wahlqvist et al., 2012	Cohort study	Incident PD risk in T2DM increases 2.2-fold. Sulfonylureas further increase risk by 57%, which is avoided by combination with metformin
Exendin-4	Shi et al., 2019	Retrospective longitudinal cohort study	Long-term metformin therapy (> 2 years) was associated with a lower incidence of PD among elderly veterans with T2DM
	Aviles-Olmos et al., 2013	Single-blind clinical trial	Improvements of the motor and cognitive measures in PD patients
	Athauda et al., 2014	Double-blind, placebo-controlled clinical trial	Confirmation of the efficacy of the Exendin-4
Liraglutide	Athauda et al., 2019	Post-hoc analysis of the double-blind trial	Efficacy of Exendin-4 treatment is higher in patients with earlier disease
	Clinical Trial not yet completed	ClinicalTrials.gov Identifier: NCT02953665	

PD: Parkinson's disease; T2DM: type 2 diabetes mellitus.

## Review

experimental studies and clinical trials in humans, leaving still undisclosed whether and when this functional link becomes a dangerous liaison. However, increasing pieces of evidence support the relationship between T2DM and PD and the crucial role that insulin and DA exert to each other, possibly opening a new possibility to treat the two diseases.

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