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Parkinson's Disease, Diabetes and Cognitive Impairment

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Word count (Abstract): 217

Word count (Paper): 4,431

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ABSTRACT

Background: Parkinson's disease is a chronic neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons. The pathophysiological mechanisms underlying Parkinson's are still unknown. Mitochondrial dysfunction, abnormal protein aggregation, increased neuroinflammation and impairment of brain glucose metabolism are shared processes among insulin-resistance, diabetes and neurodegeneration and have been suggested as key mechanisms in development of Parkinson's and cognitive impairment.

Objective: To review experimental and clinical evidence of underlying Parkinson's pathophysiology in common with diabetes and cognitive impairment. Anti-diabetic agents and recent patents for insulin-resistance that might be repositioned in the treatment of Parkinson's also have been included in this review.

Method: A narrative review using MEDLINE database.

Results: Common antidiabetic treatments such as DPP4 inhibitors, GLP-1 agonists and metformin have shown promise in the treatment of Parkinson's disease and cognitive impairment in animals and humans. Study of the pathophysiology of neurodegeneration common between diabetes and Parkinson's disease has given rise to new treatment possibilities. Patents published in the last 5 years could be used in novel approaches to Parkinson's treatment by targeting specific pathophysiology proteins, such as Nurr1, PINK1 and NrF2, while patents to improve penetration of the blood brain barrier could allow improved efficacy of existing treatments.

Conclusion: Further studies using GLP-1 agonists and DPP-4 inhibitors to treat PD are warranted as they have shown promise.

Key-words: Cognition, Diabetes, DPP-4, GLP-1, Insulin Resistance, Neurodegeneration, Parkinson's.

Short running title: Parkinson's, Diabetes and Cognitive Impairment.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting 8–18 per 100,000 people per year [1]. It is clinically characterised by the motor symptoms of bradykinesia, rigidity, tremor, and postural instability, and by non-motor symptoms such as mood disorders, cognitive impairment and autonomic dysfunction [2, 3]. It has been shown that cognitive impairment exists in as many as a third of newly diagnosed PD patients [4, 5], and after 5 years that number had increased to 50% having mild cognitive impairment (MCI) [5]. Furthermore, 26% of those with mild cognitive impairment were shown to develop Parkinson's Disease Dementia (PDD) within 5 years [5]. Mild cognitive impairment in PD is associated with a worsening quality of life, with PDD having a greater impact still [6]. The cardinal pathological characteristic of PD is the progressive loss of dopaminergic neurons in the substantia nigra *pars compacta* [7], however, lines of evidence from *in vivo* molecular imaging research has demonstrated that PD pathology involves also non-dopaminergic systems such as the serotonergic [8-10]. Serotonergic pathology in PD has been associated with the development of tremor [11,12], dyskinesias [13-15] and various non-motor symptoms [16-18].

Type 2 diabetes mellitus is characterised by impaired glucose metabolism and subsequent hyperglycaemia due to the inability of the body to mount an appropriate insulin response [19,20]. Prior to the development of hyperglycaemia, patients at risk of developing diabetes display a resistance to the effects of insulin, which is initially compensated for by increased insulin secretion from the beta-cells of the pancreas. Eventually, the ability of the pancreas to compensate for an increasing insulin-resistance reduces, resulting in hyperglycaemia [19]. The extent of the impaired glucose metabolism is assessed based on the ability of the body to normalise glucose levels after eating. Current criteria for this assessment is divided into diabetes, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) (Table 1) [21].

The prevalence of diabetes in PD is unclear, but a recent meta-analysis of population based cohort studies has shown a 38% increase in the risk of developing PD in patients with diabetes [22]. Diabetes has been linked to cognitive impairment in both PD and Alzheimer's disease (AD) [23, 24]. A case control study showed that PD patients with insulin-resistance have a two-folded increased risk of developing dementia [25]. By using positron emission tomography (PET) molecular imaging, it has been demonstrated that while there was a greater degree of cognitive impairment in PD patients with diabetes compared with PD patients without diabetes, there were no differences in nigrostriatal or cortical cholinergic PET markers [24]. These findings suggest that the effect of diabetes on cognitive impairment in PD is not related to the known neurodegenerative changes of PD and it is therefore possible that other underlying pathological processes may exist, causing the association between diabetes, PD and cognitive impairment.

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This paper looks to expand on recent reviews summarising the growing evidence linking diabetes and neurological disease [26,27]. The underlying pathophysiology common between diabetes, PD and cognitive impairment is discussed, with additional emphasis given to the evidence for the use of anti-diabetic agents in PD and on recent patents which may be used in the treatment of PD.

Pathophysiology

The association between PD and diabetes could be the result of several overlapping pathways characterising neurodegeneration and insulin-resistance. In an animal model of insulin-resistance using rats fed on a high fat diet, increased peripheral insulin-resistance and oxidative stress was accompanied by a decreased dopamine release and clearance [28]. Morris and colleagues [28] found a correlation between higher levels of insulin-resistance and greater dopaminergic dysfunction. Furthermore, using T2*-weighted Magnetic Resonance Imaging (MRI) sequences, they found an increased iron deposition in the substantia nigra. This was associated with an increased expression of iron transport proteins such as transferrin and transferrin receptor 2 in rats fed on a high fat diet compared to those fed on chow [28]. In addition, since insulin crosses the blood brain barrier [29], and insulin receptors exist in the substantia nigra [30], it was suggested that the higher levels of insulin, resulting from a high fat diet, might alter iron transport in the substantia nigra [28].

High mitochondrial iron content has been previously linked to increased oxidative damage, and it is known that impaired mitochondrial complex I function is associated with PD [28,31]. Mitochondrial dysfunction has also been specifically linked with impaired cognitive function in PD. Gatt and colleagues found that, in post-mortem tissue samples, mitochondrial complex I activity was reduced in the prefrontal cortex of patients with PDD compared to PD patients without dementia [30]. Complex I expression, however, was unchanged. Furthermore, no correlation was found between PD duration and complex I activity in either PD or PDD patients [32].

In keeping with our growing understanding of the role of mitochondria in the pathophysiology of Parkinson's disease, there is a well-established link between parkin protein and PD. Parkin is an E3 ubiquitin ligase, the mutation of which results in autosomal recessive juvenile PD [33,34]. In sporadic PD, post-translational modification of parkin results in the accumulation of toxic substrates and neuronal death [33]. While not fully understood, the role of parkin is to monitor the quality of mitochondria and trigger mitophagy when they become dysfunctional [34,35]. This occurs in part by parkin regulating PGC-1α and Parkin Interacting Substrate (PARIS). PGC-1α inhibits the production of reactive oxygen species (ROS), as well as elevating mitochondrial respiration. This occurs by the induction of suppressors of ROS such as superoxide dismutase 1 and 2 (SOD1 and SOD2) [36], though the mechanism by which PGC-1α induces these suppressors is not completely known. Furthermore, it has been shown that treatment of mice lacking PGC-1α with 1-Methyl-4-phenyl-

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1,2,3,6- tetrahydropyridine (MPTP), a neurotoxin used in PD models, resulted in greatly increased neurodegeneration that was associated with increased oxidative damage [36]. The neuroprotective effect of PGC1-α was further demonstrated using transgenic mice overexpressing PGC-1α. This overexpression was found to attenuate the neurodegenerative effects of MPTP, with protection from the loss of dopaminergic neurons when compared to wild-type mice [37]. The same study also explored the effects of resveratrol (RSV), a compound that activates PGC-1α, on MPTP treated wild-type mice. They found that, while treatment with MPTP reduced the number of dopaminergic neurons in the substantia nigra by 44%, treatment with RSV increased the number of neurons to 83% that of the control group [37]. Analysis of gene sets involved in mitochondrial function and glucose metabolism showed that at least 10 gene sets were also associated with PD. These gene sets were also under the control of PGC-1α, further supporting a role for PGC-1α in PD [38]. PARIS suppresses expression of PGC-1α, and it is increased in the substantia nigra of parkin-mutation and sporadic PD, suggesting increased PARIS levels may cause neurodegeneration [39]. Mutation of another protein, PTEN-induced putative kinase 1 (PINK1), has also been shown to result in autosomal recessive juvenile PD. PINK1 interacts with parkin by recruiting parkin from the cytoplasm to the mitochondria [40]. A recent study has shown that levels of parkin were reduced in the substantia nigra of two diabetic mouse models: high fat diet and $Lepr^{db}/Lepr^{db}$ (db/db). However, whereas levels of parkin were also reduced in the striatum and cortex of db/db mice, they were not reduced in the striatum or cortex of high fat mice [33]. This suggests that that substantia nigra is more susceptible to the effects of insulin-resistance than the striatum or cortex [33]. The reduction in parkin also resulted in the downregulation of PGC-1α and accumulation of PARIS. Indeed, the earliest sign of insulin-resistance is believed to be a reduction in the expression of PGC-1α [33,41]. Interestingly, in this model, metformin was able to restore levels of parkin and PGC-1α to normal and, although the authors were not able to suggest a mechanism by which this might take place, we can speculate that the metformin-induced improvement of insulin-resistance might underlie this phenomenon [33].

There is growing evidence suggesting that an increase in advanced products of glycosylation (AGE) is also a key component of the relation between diabetes and neurodegeneration. The formation of AGEs is increased in diabetes due to hyperglycaemia [42]. AGEs can induce protein aggregation and inflammation in the brain through the formation of (ROS) [43]. In AD, Amyloid β (Aβ) and tau protein, which are associated with the development of both senile plaques and neurofibrillary tangles (NFT), are influenced by AGEs [44]. The polymerization of Aβ, a major component of senile plaques, is enhanced by AGE mediated protein cross-linking. Tau protein is glycated, and able to induce oxidative stress, thus contributing to the formation and toxicity of NFT [44]. In PD, glycation of α-synuclein may be one of the mechanisms underlying the abnormal agglomeration of α-synuclein that leads to the development of Lewy bodies [44]. This phenomenon might also be related to the activation of the receptor for advanced products of glycosylation (RAGE), found ubiquitously on neurons. They respond to a variety of different AGEs, and are upregulated in response to inflammation [45],

and linked to increased oxidative stress [46]. The pro-inflammatory nuclear factor kB (NFkB) pathway is also enhanced by RAGE-activation [45]. Furthermore, NFkB has been shown to increase expression of RAGE, further potentiating its inflammatory effect [46]. Inflammation of the brain has been linked to many neurodegenerative diseases, including PD and, although neuroinflammation is an integral part of immune response in the central nervous system, persistent and uncontrolled inflammation eventually results in necrosis of neurons, and therefore resulting in neurodegeneration [47].

Brain-derived neurotrophic factor (BDNF) has attracted significant interest for its role in cognitive impairment in particular. BDNF is a growth factor which induces long-term potentiation (LTP) and neuronal survival [48]. BDNF is expressed in the dopaminergic neurons of the substantia nigra, and in PD this expression is reduced [49,50]. The association of BDNF with PD was demonstrated further by Wang and colleagues, who showed that serum BDNF levels were decreased in PD, and that patients with lower serum BDNF levels had worse cognitive function [50]. A functional polymorphism of BDNF, known as Val66Met, has been shown to impair hippocampal cell function in humans [51]. *In vitro* studies using cultured hippocampal neurons from rats have suggested that this occurs due to impaired BDNF secretion [51]. Altmann and colleagues assessed the association between the BDNF Val66Met and cognitive impairment in PD patients. They found that carriers of the Val66Met polymorphism had a higher frequency of cognitive impairment as assessed using the mini-mental state exam (MMSE). Additionally, those who were homozygous showing a greater frequency of cognitive impairment than heterozygotes. [52]. These findings suggest a significant role in BDNF dysfunction in neurodegeneration, and in particular cognitive impairment in PD.

In patients with diabetes, brain atrophy and vascular brain lesions, particularly small vessel disease gradually increases over time, when compared to non-diabetes patients, suggesting that diabetes could also contribute to neurodegeneration by increasing vascular brain damage [47].

A summary of the pathophysiological processes described is shown in Figure 1.

The Role of GIP, GLP-1 and DPP4

Glucose-dependent insulinotropic polypeptide (GIP) is an endogenous hormone that belongs to the incretin family. It plays a role in promoting insulin release, lowering blood glucose, and has growth factor like properties. Furthermore, there has been evidence that GIP enhances cell survival in both β-cells of the pancreas and in neurons [53]. Glucagon-like peptide-1 (GLP-1) is also an incretin hormone and analogues such as Lixisenatide, Liraglutide and Exenatide have shown neuroprotective effects in animals and humans [54-57]. Li et al provided evidence for the role of GIP in neuronal survival in animal models of PD [58]. They found that MPTP mice treated with a long acting GIP analogue showed

improved locomotor and exploratory activity. Furthermore, they demonstrated that treatment with the GIP analogue increased the levels of tyrosine hydroxylase (TH), a vital enzyme in dopamine synthesis, which is reduced in PD [58, 59]. Moreover, GIP analogue treatment decreased the loss of striatal synapses in MPTP mice [58]. Use of the GIP analogue also reduced inflammation as demonstrated by a reduction in levels of activated astroglia and microglia [58].

Ji and colleagues [60] have also demonstrated the protective effects of incretins using a protease resistant GLP-1/GIP analogue (DA-JC1) on MPTP models [60]. They found that TH levels were increased following treatment with DA-JC1 in MPTP mice and DA-JC1 was able to increase growth factor signalling molecules such as B-cell lymphoma 2 (Bcl-2) and brain derived neurotrophic factor (BDNF), and decrease apoptosis signalling molecules [60]. The pathway through which DA-JC1 conveys neuroprotection may be partially due to the activation of Akt, a growth factor signalling kinase [60]. Variability in Akt has been shown to be associated with the development of PD [61]. Furthermore, Akt is a downstream target of the insulin signalling pathway, and has been shown to have anti-apoptotic effects [61]. However, other pathways are also likely to be involved as inhibition of Akt did not fully attenuate the benefits of DA-JC1 [60]. It is likely that GLP-1 agonists also exert a neuroprotective effect by reducing vascular risk factors. Incretin therapy has been shown to improve micro and macro-vascular complications of diabetes by reducing cerebral ischaemia [62]. In addition to being effective in PD animal models, treatments with GLP-1 analogues have also resulted in improvements in memory impairment by preventing synapse loss in AD animal models [63,64], with Liraglutide being shown to have reduced the soluble Aβ oligomer [63].

The positive effects of GLP-1 analogues have been also demonstrated in humans [56,57]. An open label clinical trial using exenatide in humans demonstrated an improvement in motor and non-motor symptoms in patients with PD, as assessed using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [56]. The Mattis dementia rating scale-2 (Mattis DRS-2) was also used to assess symptoms of dementia. This supported the MDS-UPDRS assessment findings, with an improvement in cognitive function being found in patients who were given exenatide. The benefit of exenatide lasted 12 months following treatment discontinuation, suggesting that GLP-1 analogues might act on the mechanisms underlying the disease [57]. In terms of adverse effects, exenatide is generally considered to be safe, with a low rate of hypoglycaemic episodes, and few drug interactions [65]. However, in this trial, an increase in L-dopa-induced dyskinesia (LID) was noted in some patients, and required a reduction in L-dopa doses. This was unexpected, and is something that needs to be considered in any future trials. Furthermore, weight loss prevented one patient completing the trial, though this was fully reversed on cessation of exenatide. Nonetheless, the trial was generally well tolerated, with 19 of the 21 patients receiving exenatide completing the course of treatment [56].

Dipeptidyl peptidase-4 (DPP4) is an enzyme secreted by endothelial cells that catalyzes the release of an N-terminal dipeptide from polypeptides. It has enzymatic effects such as the degradation and inactivation of GIP and GLP-1, and extra-enzymatic effects including immune co-stimulation [46]. Similarly to incretins, DPP4 may play a role in promoting neurodegenerative processes. Furthermore, inhibition of DPP4 reduced neuroinflammation and improved cognitive function in diabetic animal models [66]. DPP4 inhibition also reduced the levels of ROS produced in the mitochondria of insulin resistant rats resulting in increased mitochondrial survival [66]. Additionally, treatment of high-fat fed rats with vildagliptin improved cognitive function compared to a control group. These effects were postulated by the authors to be indirectly *via* an increase in circulating and cerebral GLP-1 and GIP levels, as vildagliptin does not cross the blood-brain barrier [66]. Further studies with vildagliptin have shown an anti-parkinsonian effect on motor symptoms in rotenone rat models [44]. Vildagliptin suppresses cerebral inflammation and apoptosis by blocking the RAGE induced NFkB signalling pathway and reducing production of Tumour Necrosis factor-α (TNF-α) [44]. Vildagliptin also activated the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant signalling pathway, which attenuates NFkB mediated inflammatory responses [44]. In addition to this, vildagliptin had an anti-apoptotic effect by inhibition of the intrinsic and extrinsic pathways of apoptosis, thus preserving striatal dopamine content [44]. *In vitro* studies using vildagliptin have demonstrated anti-inflammatory effects of DPP-4 inhibitors on macrophages by inhibition of lipopolysaccharide-induced activation of NF-KB, c-Jun N-terminal kinase (JNK), inducible nitric oxide synthase (iNOS) and cytokine secretion by the macrophages [67]. In mice with transient ischaemia-reperfusion, sitagliptin reduced neuroinflammation by decreasing NF-KB, TNF-α and Interleukin-6 (IL-6) downstream inflammatory cascades [68].

Vildagliptin and sitagliptin both decreased brain oxidative stress and improved mitochondrial function therefore improving learning and memory behaviours in insulin-resistance animal models [69,70]. Insulin-resistance and subsequently object recognition in animals was improved by sitagliptin, as demonstrated by reduced plasma glucose, increased insulin concentrations and improved glucose tolerance [70]. Following treatment with sitagliptin, GLP-1 levels were increased by 60% in the plasma, and by 50% in the brain supporting the notion that DPP-4 effects are mediated *via* GLP-1 [70]. The study also showed that brain GIP concentrations were increased by 50%. An increase in GLP-1 and GIP receptor mRNA in the hippocampus after sitagliptin administration was also found [70]. This supports the possibility that in addition to GLP-1, GIP may also have a neuroprotective effect, though further studies are required to explore this possibility. The up-regulation of other proteins such as synaptophysin (SYP) and vascular endothelial growth factor (VEGF) in the hippocampus following administration of sitagliptin, as well an increase in antioxidants such as superoxide dismutase 2 (SOD2) and NrF2, provide an interesting insight into the mechanisms underlying the improvement in cognition displayed using DPP-4 inhibitors [70]. As with GLP-1 analogues, DPP4 inhibitors have also shown promise in treatment of other

conditions. Linagliptin has been shown to protect against stroke in animal models and both vildagliptin and saxagliptin attenuates the effects of steptozotocin induced-AD in rats [71-73].

In addition to the mechanisms described above, DPP-4 inhibitors are also likely to provide benefit by reducing microvascular complications associated with diabetes small-vessel disease. They are known to reduce HbA1C by 0.7-0.8%. The subsequent reduction in free radicals associated with hyperglycemia reduces vascular inflammation [46]. There is also evidence of reduced blood pressure, and improved lipid profile, which will further reduce the risk of microvascular disease [74]. Other studies have linked endothelial dysfunction and subsequent vascular dementia to diabetes and these effects have been attenuated by vildagliptin [74].

Several biologically neuropeptide has been proposed as potential target of DPP-4 inhibitors in brain but the precise one remain unclear. Pharmacological inhibition of DPP4 prevents the enzymatic cleavage of Xaa-Pro dipeptides from several substrates, thus suggesting additional, multifaceted therapeutic potential [46]. The bioactive peptides peptide histidine-methionine (PHM) and pituitary adenylate cyclase activating peptide (PACAP) have also been shown to be physiological DPP4 substrates *in vivo*. PACAP belongs to the secretin/glucagon/vasoactive intestinal polypeptide superfamily; it is widely distributed in the central and peripheral nervous systems and acts as a neurotransmitter, neuromodulator, and neurotrophic factor [46]. Other substances, such as substance P, stromal cell-derived factor 1, gastrin-releasing peptide, and C-X-C motif chemokine 10, are also supposed to be implicated in neuronal development/survival as well as in the pathophysiology of neuroinflammation, AD and/or PD. To date, however, there is no *in vivo* evidence to support an efficacy mediated relationship between DPP4 inhibition and neuroprotection by these substrates. Interestingly, recent literature has shown that: 1) DPP4 enzymes are able to truncate amyloid peptides in vitro thus promoting disaggregation of preformed fibrils, and 2) the inhibition of prolyl oligopeptidase accelerates the clearance of α-synuclein aggregates in *in vitro* and in vivo models [46]. These findings support the hypothesis that these peptides/proteins represent potential substrates for DPP4 enzymes.

DPP-4 inhibitors benefit from having an excellent safety profile, with very few adverse effects noted, in particular a low rate of hypoglycaemic episodes [75]. They are also available as oral preparations compared to GLP-1 agonists, making them more universally accessible to patients who cannot self-inject [75]. In addition, different DPP-4 inhibitors are hepatically or renally metabolised, which may broaden their use in patients with co-existent liver or renal disease. These properties make them an excellent candidate, though further study is needed to fully assess their impact on patients who are often complex and on multiple drugs. Pharmacokinetics characteristics of GLP-1 agonists and DPP4 inhibitors are shown in Table 2.

Metformin

Metformin is one of the first-line treatments used in diabetes. It is well-tolerated and not associated with weight gain or high risk of hypoglycaemia. It improves hyperglycaemia by decreasing hepatic glucose production, decreasing intestinal glucose absorption and increasing insulin sensitivity [76]. These effects are partially mediated by activation of AMP-activated protein kinase (AMPK). AMPK has several roles, including regulating cell survival in response to hypoxia or oxidative stress [77]. A recent study showed that AGEs induce the death of human neural stem cell (hNSCs) by down-regulating AMPK and its downstream pathways. Metformin showed a protective effect on hNSCs by enhancing AMPK. Furthermore, AMPK induces PGC1α, which promotes mitochondrial function, and as would be expected, an increase in mitochondrial function was demonstrated [77]. α-synuclein overexpression and elevated extracellular levels of α-synuclein also downregulate AMPK activation in *in vitro* models, and restoring the AMPK activity reduces α-synuclein toxicity [78].

Given the pivotal role α-synuclein in PD pathology, this provides promising evidence that metformin could attenuate some of the pathological effect of α-synuclein in PD patients. Metformin was shown to have an anti-oxidant effect by a study using mice with catalepsy induced by haloperidol [79]. Following induction of catalepsy with haloperidol, a fall in glutathione and catalase levels and a reduction in superoxide dismutase (SOD) activity was observed. These are all known to have important anti-oxidant effects. However, treatment with metformin significantly increased the levels of glutathione and catalase, and improved SOD activity. There was also an improvement in catalepsy, and the authors postulated that this was due, at least in part, to a reduction in oxidative stress induced by the treatment [79]. The neuroprotective effects of Metformin were also evaluated *in vivo* using high fat diet fed mice [80]. In this model, improving glycemic control following treatment with metformin was associated with a decrease in plasma oxidative stress, complete eradication of brain oxidative stress, improvement in mitochondrial dysfunction and protection against mitochondrial swelling [80]. ROS are known to open the mitochondrial permeability transitional pore (mPTP) and when opened, the mPTP can result in mitochondrial swelling [81]. The author postulated that the reduction in ROS following metformin treatment prevented the opening of the mPTP, thereby reducing mitochondrial swelling and therefore providing a neuroprotective effect [80]. It was also demonstrated that the learning and memory impairment caused by the high fat diet was reversed following the treatment with metformin [80].

In MPTP mouse models of PD, there was improved motor function after long-term treatment with metformin [82]. Reduced oxidative stress, more TH-positive dopaminergic neurons and an increase in BDNF were also demonstrated and this was similar to the effect shown using the incretin analogue DA-JC1 [60, 82]. This suggests a possible overlap in the pathway by which metformin and incretins exert a neuroprotective effect. The only study in humans is a prospective

cohort study conducted in Taiwan that shows a 2.2-fold increases risk of PD in diabetic patients. The addition of sulpho-nylureas increased the risk by a further 57%. However, use of metformin attenuated the increase in risk associated with the use of sulphonylureas. The reason of the reduction of PD risk in diabetes treated with metformin is still unclear, although there are several pathological mechanisms (described above) that might be implicated with the progression of PD and that are affected by the treatment with metformin [83].

Nonetheless, not all evidence has suggested that metformin is beneficial in neurodegenerative conditions. A case-control study based in the United Kingdom suggested that metformin may be associated with an increased risk of AD in long-term use [84], and treatment of mice with metformin has been shown to increase tau protein aggregation [85]. However, the same study does also show metformin to reduce tau phosphorylation, leading to the authors concluding that the ben-efits are mitigated by negative effects, rather than metformin having an overall detrimental effect [85].

Other factors which may limit the use of metformin in the future are its side effects and interactions. Metformin is associated with lactic acidosis, and is renally excreted, therefore it is used with caution in patients with renal impairment [86]. Furthermore, anticholinergics increase the oral bioavailability of metformin by altering gastrointestinal motility. As anticholinergics are commonly used in neurological disease, this may limit the use of metformin in the future. Metformin is also known to reduce vitamin B12 absorption, and this may exacerbate some neurological disease [65]. However, metformin does not cause weight gain or loss, is not associated with hypoglycaemia and is otherwise considered to be a largely safe drug.

Overall, the evidence suggests that metformin has a neuroprotective effect which may be of use in treating a wide range of neurodegenerative conditions. The reason of the reduction of PD risk in diabetes treated with metformin is still unclear, although there are several pathological mechanisms (described above) that might be implicated with the progression of PD and that are effected by the treatment with metformin [83].

Thiazolidinediones

Thiazolidinediones are a class of oral hypoglycemic agents commonly used in treatment of diabetes. They exert their effect by acting on the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ). Pioglitazone, the most commonly used thiazolidinedione, provides neuroprotective effects in MPTP mice and lipopolysaccharide models of PD by reducing oxidative stress and microglial activation [87]. A double-blind, randomized controlled trial of the effects of pioglitazone on PD patients showed that pioglitazone was not able to slow down disease progression [88]. However, cognitive function was not assessed in this trial. There have been several studies, using both rosiglitazone and

pioglitazone, which have demonstrated improvement in cognition of animal models of diabetes [89]. However, a pilot study examining the effects of pioglitazone on the cognition of elderly patients with mild cognitive impairment did not show any improvement on cognitive performance [90], suggesting that thiazolidinediones are not the best candidates to slow neurodegeneration in diabetes and PD.

Thiazolidinediones are associated with several adverse effects which have limited their use in recent years. They have been linked to an increase risk of fractures, while rosiglitazone has been shown to increase the risk of heart failure and myocardial infarction [86]. As the demographic of a PD patient is likely to be older and therefore at a greater cardiovascular risk, and the disease by its very nature increases the likelihood of falls, these adverse effects are likely to be unacceptable unless great benefit is demonstrated. Furthermore, thiazolidinediones are hepatically metabolised [91], and therefore predisposed to the effects of enzyme inducers and inhibitors which may affect plasma concentrations and therefore increase adverse effects or reduce clinical benefit.

Sulphonylurea

Sulphonylreas are amongst the most commonly used class of hypoglycemic drugs. They stimulate pancreatic β-cells to release insulin [75]. However, unlike other diabetic therapies, their use in cognitive impairment and neurodegenerative conditions has not been greatly investigated. We found only one study evaluating the association between sulphonylureas and PD (described above) that showed an increased the risk of PD in diabetics taking sulphonylureas [83]. However, it has been demonstrated that glimepiride, but not glipizide, confers a neuroprotective effect in AD [92]. It was hypothesised that the difference exists because glimepiride activates endogenous glycosylphosphatidylinositol-phospholipase C (GPI-PLC) while glipizide does not. *In vitro* neurons were damaged by Aβ before being treated with glimeperide. Following treatment, a reduction in Aβ induced synapse damage was observed [92]. Selectively inhibiting GPI-PLC reversed the protective effect of glimepiride, supporting the hypothesis that protective effect of glimepiride is due to activation of GPI-PLC [92]. Other studies have shown that glimepiride may exert its neuroprotective effect by serving as an agonist of PPAR-γ [93]. Use of a PPAR-γ antagonist reversed the neuroprotective effect on primary cortical neurons damaged with Aβ *in vitro.* Streptozosin-induced diabetic rats were observed to undergo sustained chronic oxidative stress in the brain due to hyperglycaemia. This was demonstrated by an increase in the total oxidant status (TOS), malondialdehyde (MDA) and oxidative stress index (OSI) [94]. Treatment with gliclazide attenuated this effect by reducing TOS and OSI levels [94].

The future use of sulphonylureas is likely to be inhibited by their significant adverse effects and their vast interactions with other drugs. They have a high bioavailability, are rapidly absorbed, and are metabolised by the liver, particularly the enzyme cytochrome P2C9, before being renally excreted. They are prone to liver enzyme inducing and inhibiting drugs, including those commonly seen such as trimethoprim and carbamazepine. This can put the patient at risk, particularly as inhibition of liver metabolism can result in potentially dangerous hypoglycaemic episodes in vulnerable patients [65,75]. Furthermore, sulphonylureas are associated with weight gain [75], which may be undesirable in a patient who is already struggling with mobility.

A summary of classes' anti-diabetic therapies and their possible mechanisms of neuroprotection in humans is shown in Table 3.

Current and Future Developments

The risk of PD seems to be increased in people with diabetes. Anti-diabetic treatment has shown a protective effect on animal models of PD and in a few clinical studies. Among them, DPP4 inhibitors seem to be the potential candidate for future trials aimed to slow PD progression, though a few challenges still need to be faced. DPP4 inhibitors offer lower penetration of the blood brain barrier compared to GLP-1 agonists. However, the effects of DPP4 inhibitors appear to be *via* increases in both GLP-1 [66,70] and GIP [70] and this could lead to an augmented neuroprotective effect as shown on animal models of PD [44]. DPP-4 inhibitors are orally administered and generally well tolerated, with a lower incidence of hypoglycemia and no weight gain compared to GLP-1 analogues, making them popular for use in conjunction, or as an alternative to metformin in diabetics. In addition, some DPP-4 inhibitors are excreted by kidney, while others are hepatically metabolized. As a result, the potential for their use in those with either renal or liver impairment is greater, so that a greater range of patients could benefit from them [75]. To the best of our knowledge, there have been no ongoing human trials using DPP-4 inhibitors to alleviate symptoms of PD, similar to those performed using the GLP-1 analogue exenatide. If a human trial does take place in the future, care must be taken with regards to the dose of L-dopa, as this was affected by exenatide [56], and it is possible DPP-4 inhibitors may have a similar impact.

A better assessment of the neuroprotective effects of DPP-4 inhibitors is limited by its inability to pass the blood-brain-barrier. Recent patents have offered potential solutions to this. Development of a dual variable domain binding protein that binds antigens expressed on the brain vascular epithelium and thus facilitates the uptake of a composition into the brain may provide a solution and in doing so, allow further study of the neuroprotective effects of DPP-4 inhibitors outside of their action *via* GLP-1 and GIP [95,96]. An alternative solution to this challenge has been proposed by another patent, which suggests the use of intranasal administration as a method of bypassing the blood-brain-barrier. This is achieved

by use of a pharmaceutically active agent-transport moiety complex which bypasses the blood-brain barrier *via* the intranasal route [97].

The improved understanding of the pathophysiology in PD has also offered the opportunity for more novel treatment methods. As discussed in this review, mitochondrial dysfunction and oxidative stress play an important role in neurodegeneration, and new methods acting on these pathways are under developed. PINK1 is essential in the recruitment of parkin to mitochondrial cytoplasm, and its mutation results in autosomal recessive juvenile PD [40]. A recent patent suggested to target a molecule which modulates the activity of PINK1, acting as agonist, and thus increasing the signalling pathways triggered by PINK1. This offers a potential avenue for the treatment of PD, but will require experimental studies [98].

Reducing oxidative stress is a viable approach to the reduction of neurodegeneration given the evidence demonstrating the role of oxidative damage. A patent for Curcumin which can pass the blood brain barrier and offers protection from oxidative stress was published in 2014. It demonstrates an ability to restore BDNF levels and up-regulate NrF2 [99]. Both of these have been shown to play a role in neurodegeneration in PD animal models, and BDNF dysfunction in particular is associated with cognitive impairment. Therefore, it is possible that restoration of BDNF levels may not only improve symptoms of PD, but cognitive impairment in particular.

The cardinal pathology of PD remains the loss of dopaminergic neurons, and restoration of this remains a key component of treatment. A patent for a nuclear receptor subfamily 4, group A, member 2 (Nurr1) receptor agonist also shows promise. Nurr1 modulates the regulation of genes coding for TH [100], and Nurr1 agonists may restore TH activity, thus increasing dopaminergic function [101].

Conclusion

Diabetes and insulin resistance are associated with an increased risk of PD. There is increasing evidence that treatments established in the management of diabetes slow the neurodegenerative process and might be potential candidates for repositioning for the treatment of neurodegenerative disorders such as PD and AD. Given increasing evidence and their good safety profile, GLP-1 agonists and DPP-4 inhibitors are particularly promising for testing in novel clinical trials aiming to provide disease modification in PD, though before trials can proceed, more evidence needs to be collected on potential adverse effects and drug interactions as the target patients are often very complex. Furthermore, the use of anti-diabetic drugs has expanded our understanding of the pathophysiology underlying diabetes, PD and cognitive impairment.

This improved understanding will continue to open potential therapeutic avenues, with new patents being developed to exploit them.

Figure Legend

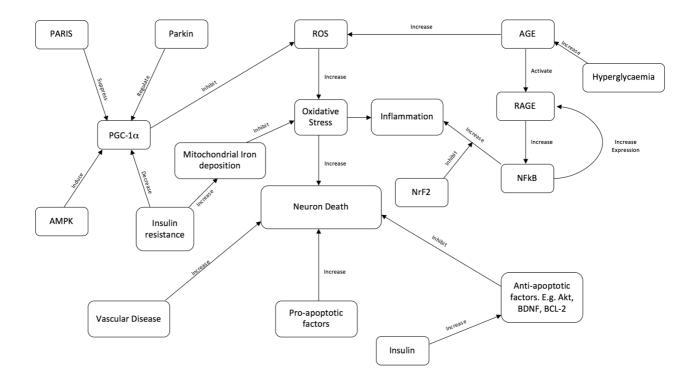**Figure 1.** A summary of the pathophysiological processes underlying neurodegeneration.

Table 1: Diagnostic criteria for diabetes, impaired glucose tolerance and impaired fasting glucose[a].

	Criteria	
	Fasting venous plasma Glucose	**2-h Venous plasma glucose***
Diabetes	≥7.0mmol/L	11.1 mmol/L
Impaired Glucose Tolerance	≤7.0mmol/L	≥7.8 and <11.1 mmol/L
Impaired Fasting Glucose	6.1-6.9 mmol/L	<7.8 mmol/L

[a] See text for reference.

*Venous plasma glucose level taken 2 hours after 75g oral glucose load.

Table 2: Pharmacokinetics characteristics of GLP-1 agonists and DPP4 inhibitors

GLP-1 AGONISTS			
Drug	**Doses**	**Half-life**	**Excretion**
Exenatide	5-10 mcg bid	Short	Renal
Liraglutide	0.6-1.8 mg once	Long	Metabolized by DDP4 and endopeptidase (no renal)
Lixienatide	Uncertain (probably 20 mcg/day)	Short	Renal
Albiglutide	Uncertain (30 mg/week)	Very long	Renal
Dulaglutide	Uncertain	Long	Renal
DPP-4 INHIBITORS			
Sitagliptin	100 mg once	Long	Renal
Vildagliptin	50 mg bid	Short	Renal (50%) and Metabolized by DDP4 and endo-peptidase (50%)
Saxagliptin	5 mg once	Short (but active metabolite)	Renal
Alogliptin	12.5–25 mg once	Long	Renal
Linagliptin	5 mg once	Very long	Metabolized by DDP4 and endopeptidase (no renal)

Table 3: Summary of classes' anti-diabetic therapies, their possible mechanisms of neuroprotection and available human data.[a]

Class of drug	Proposed mechanisms of neuroprotection	Human clinical study data
GLP-1 agonist	Increase TH levels. Increase Bcl-2, reduce BAX. Activation of Akt. Reduction in soluble Aβ oligomer. Reducing risk of vascular disease.	Single-blind trial with exenatide and PD patients. Results showed improved motor function and cognition. No improvement in depression/Quality of Life. Benefits persisted 12 months post-trial. Adverse effects included L-dopa induced dyskinesia and weight loss.
DPP-4 inhibitor	Blocking the RAGE induced NFkB signalling pathway by reducing production of TNF-α. Activating the Nrf2-antioxidant signalling pathway. Inhibition of lipopolysaccharide induced activation of NF-KB, JNK and iNOS and cytokine secretion macrophages. Increase in SOD2 and NRf2 in hippocampus. Reducing risk of vascular disease.	No
Metformin	Activating AMPK and inducing PGC1a. Reducing mitochondrial swelling. Increasing catalase and glutathione levels. Increasing activity of SOD. Increase in TH.	Study in Taiwan showed that metformin reduced the risk of developing PD in patients with DM. Study in United Kingdom showed increased risk of AD.

Thiazilidiones	Reduce oxidative stress. Reduce microglial activation.	Double-blind randomised controlled trial showed no improvement in PD symptoms with Pioglitazone. Pilot study with elderly patients with mild cognitive impairment given pioglitazone showed no improvement in cognition.
Sulphonylurea	Activation of GPI-PLC by glimepiride.	No

^a See text for references.

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