Growing evidence suggests drugs that can activate the glucagon-like peptide 1 receptor can modulate several pathological processes underlying Parkinson's disease. Here, we review the molecular mechanisms underlying these potential neuroprotective effects.

The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: mechanisms of action

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Growing evidence suggests that agonists of the glucagon-like peptide 1 (GLP-1) receptor provide neuroprotection across a range of experimental models of Parkinson's disease (PD) and, recently, a small proof-of-concept, open-label human trial of exenatide in the treatment moderate severity PD appeared to show persistent improvements in motor and cognitive function. The underlying mechanisms of action remain unclear, but as evidence for the potential use of GLP-1 agonists in treating several neurodegenerative disease mounts, and with several clinical trials of GLP-1 analogues in PD and Alzheimer's disease (AD) currently underway, here we review the molecular mechanisms underlying the neuroprotective effects of GLP-1 analogues in the laboratory and their potential therapeutic utility with particular relevance to PD and PD dementia (PDD).

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and affects 1.5% of humans over 65 years of age globally. Current treatments are aimed at dopamine (DA) replacement and, although these treatments can initially be effective in relieving motor symptoms, over time complex motor fluctuations and dyskinesias can occur, which negatively impact patients' quality of life and mobility. Although more advanced therapies, including continuous intraduodenal infusion of levodopa, subcutaneous apomorphine infusions, and deep brain stimulation, have varying levels of success at minimising these motor complications, they ultimately have no effect on altering the progressive nature of the disease. Furthermore, over time, the involvement of nondopaminergic systems influences the onset of features such as depression, gait difficulties, and dementia, which are often refractory to treatment and have profound effects on patients' quality of life. Therefore, an urgent goal is to develop effective neuroprotective treatments that target pathways common to neurodegeneration and affect both dopaminergic and nondopaminergic systems and, therefore, that could slow the progression of the disease.

The incretin hormone glucagon-like peptide 1 (GLP-1) is best known for its effects on glucose homeostasis and facilitation of insulin signalling and, as such, agents that activate the GLP-1

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GLOSSARY

Amyloid beta (Aβ) peptides of 36–43 amino acids that are the main component of the amyloid plaques found in the brains of patients with AD.
Alpha-synuclein a major component of Lewy bodies, the pathological correlate found in the brains of patients with PD.
Insulin resistance a condition describing the reduced responsiveness of cells to the action of insulin.
Insulin receptor substrate 1 (IRS-1) a critical component of intact insulin signalling; phosphorylation of IRS-1 on serine residues prevents insulin/IGF-1 binding to the IR and subsequent activation of downstream effectors.
Microglial cells resident macrophages in the CNS that mediate a balance between neuroprotection and neurotoxicity; when activated, they can express a cytoprotective M2 phenotype generally providing trophic support and inhibiting inflammation; however, continuous exposure to stress and prolonged microglial activation can lead to polarisation towards the cytotoxic M1 phenotype, causing production of superoxide proinflammatory cytokines that leads to progressive oxidative stress cell death.

receptor (GLP-1R), such as GLP-1 analogues or dipeptidyl peptidase 4 (DPP-IV) inhibitors, have been developed for use in the treatment of type 2 diabetes mellitus (T2DM). Accumulating evidence suggests that these GLP-1 analogues exert several extrapancreatic effects independent of glucose homeostasis and can cross the blood–brain barrier (BBB) to influence several cellular pathways, such as neuroinflammation, mitochondrial function, and cellular proliferation, within the central nervous system (CNS). Furthermore, a growing number of studies have demonstrated neuroprotective effects of GLP-1 R stimulation in models of PD, resulting in improvements in motor and non-motor deficits.

The neuropathophysiology underlying cognitive decline in PD remains unclear, although deposition of Lewy body-related pathology in neocortical and limbic areas is thought to represent one of the most significant factors. However, accumulating evidence suggests that Alzheimer's disease (AD)-type pathology is undoubtedly relevant for at least a subset of individuals with PD dementia (PDD) due to either superimposed AD-type pathology, or because of an interaction between amyloid β (Aβ) and the rate of progression of cortical Lewy body and/or alpha synuclein pathology [1]. In this review, we discuss the effects of GLP-1R stimulation with respect to PD and, where relevant, the evidence emerging from research into GLP-1 stimulation and AD-related pathology. We then follow by reviewing the proposed mechanisms underlying its effects.

The GLP-1 signalling pathway

GLP-1 is an endogenous 30 amino-acid multifunctional peptide first recognised for its role in mediating the 'incretin' effect. Secreted from L cells in the small intestine in response to food ingestion, it stimulates glucose-induced insulin secretion, insulin biosynthesis, slows gut emptying, and inhibits glucagon secretion, to mediate glucose homeostasis. In additional to its metabolic effects, it also exerts trophic effects, namely enhancing islet beta cell proliferation differentiation, inhibiting apoptosis, and enhancing cell survival, thus regulating B cell mass [2,3].

A small amount of GLP-1 is also produced in the brain, released from hypothalamic nuclei from nerve endings with cell bodies in the nucleus of the solitary tract and caudal brainstem that project to cortical, hypothalamic, and hippocampal nuclei. In its role as a neuropeptide, GLP-1 can diffuse within the brain to regulate many autonomic and neuroendocrine functions, including promoting satiety, pancreatic secretions, slowing gastric emptying, and regulating blood pressure and heart rate [4].

The actions of GLP-1 are mediated by GLP-1R, a seven-transmembrane spanning G-protein-coupled receptor (GPCR) that, although mainly expressed in pancreatic islets, is also selectively expressed throughout the brain, with high densities in the frontal cortex, hypothalamus, thalamus, hippocampus, cerebellum, and substantia nigra [5,6]. Similar to islet cells that can upregulate GLP-1 expression under stressful conditions, such as T2DM [7], it was recently demonstrated that microglial cells can also increase GLP-1 and GLP-1R expression in response to inflammatory stimuli [8], suggesting that endogenous GLP-1 is a natural response to limit harmful stimuli.

Following activation of the alpha subunit of the GPCR, adenyl cyclase is activated, leading to an increase in intracellular cAMP, which then activates protein kinase A (PKA) and phosphoinositide 3-kinase (PI3K), which phosphorylates and activates a variety of downstream signalling pathways. These pathways can be simplified into two branches: (i) the mitogen-associated protein kinase/extracellular signal-regulated kinase (MAPK/ERK; also known as Ras-Raf-MEK-ERK); and (ii) PI3K/protein kinase B (AKT) pathways [9]. An important downstream target of GLP-1 signalling is the AKT pathway, which acts as a major regulator of physiological responses to normal ageing. AKT has the ability to phosphorylate over 50 substrate proteins, such as glycogen synthase kinase 3 beta (GSK-3B), Forkhead box protein O1 (FOXO1), and mammalian target of rapamycin (mTOR), and can modulate several cellular processes found to be disrupted in PD, such as protein synthesis, apoptosis, inflammation, mitochondrial biogenesis, and autophagy. Broadly speaking, activation of these pathways promotes cellular survival, while inhibiting proapoptotic pathways (Fig. 1). Further details of the relation between these processes and PD pathogenesis are discussed in subsequent sections of this article.

Unfortunately, endogenous GLP-1 is rapidly rendered inactive by circulating enzyme dipeptidyl peptidase IV (DPP-IV) into a metabolite that has no activity against GLP-1R [10–12]. However, the discovery of a naturally occurring GLP-1 agonist resistant to DPP-IV degradation, named exendin-4, in the saliva of the Gila monster (*Heloderma suspectum*), a venomous lizard native to the south-western USA and Mexico, has allowed researchers to circumvent this obstacle. Subsequently, synthetic versions of exendin-4 and several other GLP-1 analogues have since been developed [13] for use in diabetes to utilise their insulinotrophic actions and include exenatide, liraglutide, lixisenatide, and dulaglutide. These GLP-1 analogues have significantly longer half-lives than endogenous GLP-1 and exert a dose-dependent pharmacological effect that can raise circulating levels of endogenous GLP-1 levels eightfold [14]. Apart from dulaglutide, these peripherally administered drugs are all also able to penetrate the BBB to some degree in experimental models [15,16] to exert central effects.

Representing an alternative approach to GLP-1R stimulation, orally administered drugs have been developed more recently that

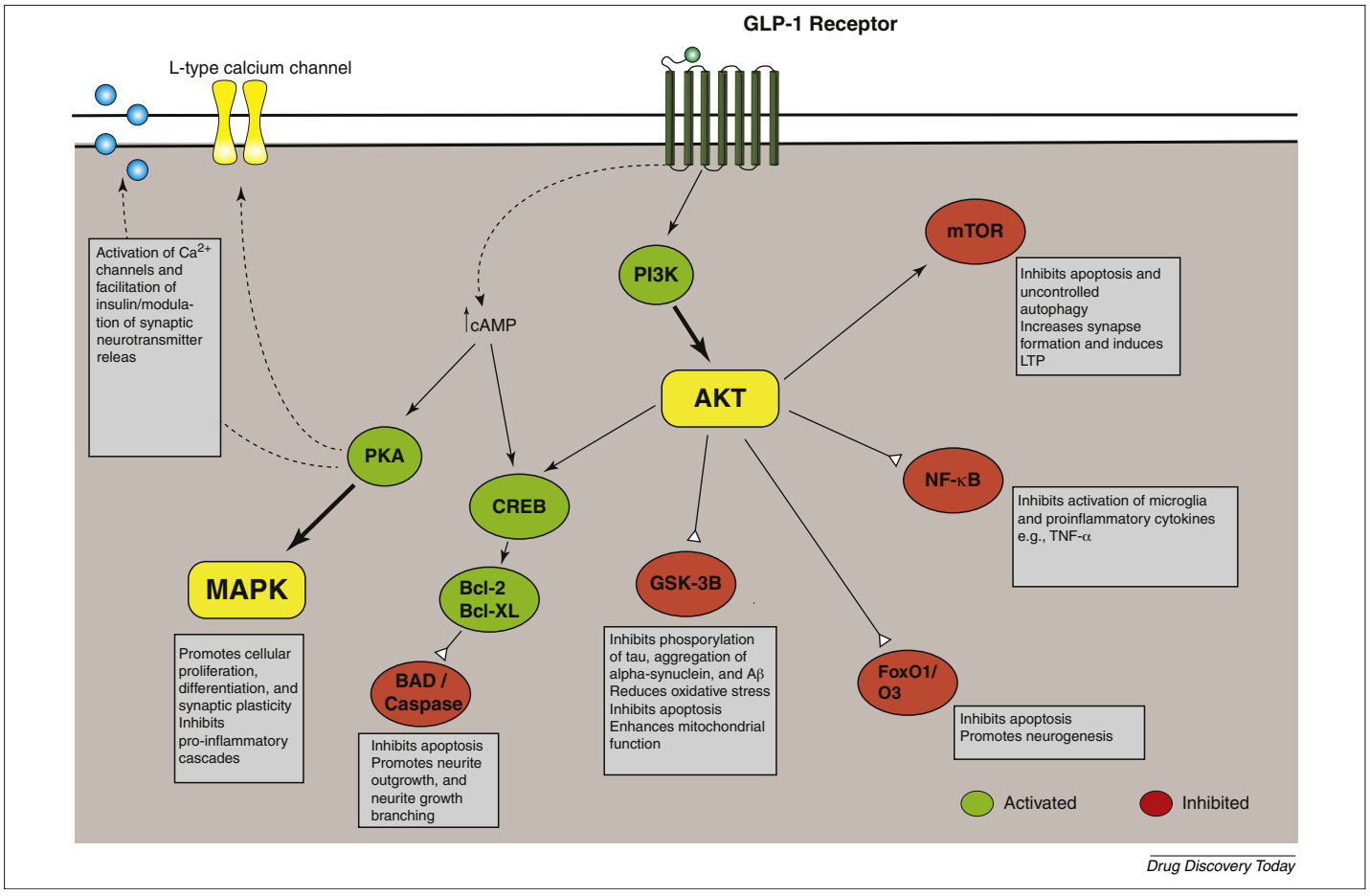

FIGURE 1

Glucagon-like peptide 1 (GLP-1) receptor activation in neurons showing the influence of downstream pathways on Parkinson's disease (PD) pathogenesis. Stimulation of the GLP-1 receptor (GLP-1R) leads to an increase in intracellular cAMP, which then activates protein kinase A (PKA) and phosphoinositide 3-kinase (PI3K), which phosphorylate and activate a variety of downstream signalling pathways that can be simplified into two branches: the mitogen-associated protein kinase/extracellular signal-regulated kinase (MAPK/ERK; also known as Ras-Raf-MEK-ERK) and PI3K/protein kinase B (AKT) pathways, which can modulate intracellular events, such as activation of calcium channels, enhancing protein synthesis, cellular proliferation, and mitochondrial biogenesis while inducing inhibition of apoptosis, inflammation, and protein aggregation, leading to improved cell survival. *Abbreviations*: Bcl-2, B cell lymphoma 2; BAD, (Bcl-2) antagonist of death; Bcl-XL, B cell lymphoma 2 extra-large; cAMP, cyclic AMP; CREB, cAMP response element-binding protein; FoxO1/O3, Forkhead box O1/O3; GSK-3B, glycogen synthase 3 beta; LTP, long-term potentiation; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TNF, tumour necrosis factor.

inhibit DPP-IV and can enhance endogenous levels of GLP-1 twofold. This class of drugs is currently used an adjunctive therapy in diabetes and includes sitagliptin, saxagliptin, vildagliptin, and linagliptin.

GLP-1R activation in models of PD and AD

In view of the influence that GLP-1R activation has on diverse cellular processes, it is perhaps not surprising that accumulating data indicate that agents that can activate GLP-1R have potential neuroprotective and neurorestorative properties across a range of experimental models of PD and AD (Tables 1 and 2). In widely used animal toxin models designed to mimic aspects of nigrostriatal degeneration seen in PD, exenatide-treated animals can halt 6-OHDA, MPTP, and lipopolysaccharide (LPS)-induced dopaminergic degeneration and restore DA imbalance, resulting in significant improvements in behaviour and motor function [17–20]. Interestingly, exenatide was also able to restore levels of other neurotransmitters depleted in PD. In a novel rodent model with dopaminergic, serotonergic, and noradrenergic deficits, exenatide administration restored levels of these neurotransmitters, leading to a reversal of neuropsychiatric dysfunction [21]. Similarly, newer GLP-1 analogues with longer half-lives (liraglutide and lixisenatide) have also demonstrated protective effects and improved motor function in the MPTP rodent model of PD [22].

However, data from DPP-IV inhibitors in experimental models of PD are conflicting. Rats pretreated with saxagliptin before the induction of rotenone-induced nigrostriatal lesions demonstrated enhanced striatal DA synthesis and reduced dopaminergic neuronal loss, resulting in improved motor performance and coordination in a rotarod test [23]. However, rats acutely or chronically pretreated with supramaximal doses of sitagliptin (a DPP-IV inhibitor with a substantially longer half-life than saxagliptin) were not protected against MPTP-induced striatal dopaminergic degeneration [24].

GLP-1 analogues have also been studied in experimental models of AD for their effects on AD-related pathology and cognition. Use

TABLE 1

Effects of GLP-1 analogues and DPP-IV inhibitors in models of PD: data from experimental models and clinical trials

Drug	Experimental data	Results and/or effects	Human data	Refs
GLP-1 analogue				
Exenatide	*In vitro* PC12 cells	Promoted NGF-initiated differentiation; rescued degenerating cells after NGF-mediated withdrawal	Open-label RCT in 45 patients which led to a mean advantage of 7.0 points on MDS-UPDRS Part III, which persisted after a 12-month 'wash-out' period, together with improvements in Mattis Dementia Rating scale and other non-motor areas [240,241]; Phase II double-blind, placebo controlled trial underway (Clinicaltrials.gov NCT01971242)	[157]
	In vitro 6-OHDA	Increased number of TH+ striatal neurons; elevated antiapoptotic proteins Bcl-2; reduced expression proapoptotic proteins caspase-3 and Bax		[16]
	Rat LPS	Post-lesioning treatment restored depletion of extracellular DA and TH activity back to normal levels, increased striatal tissue DA concentrations and number of nigral TH+ neurons, reduced apomorphine-induced rotations		[15]
	Rat 6-OHDA	Post-lesioning treatment protected DA neurons, increased striatal tissue DA concentrations and number of nigral TH+ neurons, reduced apomorphine-induced rotations		[15]
	Mouse MPTP	Prelesioning treatment preserved TH+ neurons and preserved motor function in rotarod and pole tests indistinguishable from controls		
	Mouse MPTP	Prelesioning treatment reduced loss of TH+ striatal neurons, halted microglial activation and MPTP-induced expression of matrix metalloproteinase 3, TNF-α and IL1β		[18]
	Rat 6-OHDA	Increased the number of TH- and VMAT2-positive neurons in the SN, increased and normalised amphetamine-induced rotations		[17]
	Novel rodent model with NA, SA and DA deficits	Post-lesioning treatment restored extracellular/tissue levels of DA, NA and SA and TH+ cell counts; reversed neuropsychiatric dysfunction		[19,249]
Liraglutide	Mouse MPTP	Post-lesioning treatment preserved TH+ neurons in the SN; reduced levels of BAX and increased Bcl-2; prevented motor impairment in rotarod, open-field locomotion, catalepsy tests	No human data currently	[20]
Lixisenatide	Mouse MPTP	Post-lesioning treatment preserved TH+ neurons in the SN; reduced levels of BAX and increased Bcl-2; prevented motor impairment in rotarod, open-field locomotion, catalepsy tests	No human data currently	[22]
Dulaglutide	No experimental data	No experimental data currently	No human data currently	
DPP-IV inhibitor				
Saxagliptin	Rat rotenone	Preserved SNPc TH+ neurons; decreased NF-κB, iNOS, TNF-α, ICAM-1, MPO, capase-3, increased Bcl-2, BDNF	No human data currently	[21]
Sitagliptin	Mouse MPTP	Did not prevent DA degeneration, TH depletion	No human data currently	[22]

of GLP-1 analogues has demonstrated significant effects on AD-related pathology and cognition, causing reductions in deposition of Aβ, and Aβ-induced proinflammatory responses, enhancing synaptic plasticity, hippocampal neurogenesis, and long-term potentiation (LTP), translating to improvements in cognitive deficits [25–33].

However, studies using DPP-IV inhibitors have somewhat conflicting results. Saxagliptin and sitagliptin administration caused an increase in hippocampal GLP-1 levels in rodents injected with intracerebral streptozotocin and transgenic (Tg) AD mice, respectively, accompanied by reduction in AD-related pathology and inflammatory markers and improvements in memory impairments [34,35]. However, in diabetic rats and primary cortical neurons, sitagliptin administration caused a paradoxical increase in tau phosphorylation [36].

Despite the range of neuroprotective effects seen in various models, there remains an amount of mechanistic uncertainty regarding the downstream effects of GLP-1R activation. However,

TABLE 2

Effects of GLP-1 analogues and DPP-IV inhibitors in models of AD: data from experimental models and clinical trials

Drug	Experimental model	Results and/or effects	Human data	Refs
GLP-1 analogue				
Exenatide	3 × Tg-AD mice with and without STZ-induced diabetes.	Protected neurons from Aβ oxidative-induced cell death, lowered brain levels of APP and Aβ *in vivo*; tau levels unaffected	Phase II trial evaluating exenatide in 230 patients with AD or MCI (NCT01255163) is underway	[29]
	ICV-STZ rats	Reversed ICV-STZ-induced tau hyperphosphorylation leading to better learning and memory performance in Morris water maze test		[110]
	PC12 cells treated with glucose-bovine serum albumin (BSA)	Protected neurons: reduced cell tau phosphorylation induced by high glucose		[112]
	T2DM rats	Prevented hyperphosphorylation of tau in hippocampus and improved insulin signalling		[109]
	In vitro hippocampal neurons and mice	Reduced levels of Aβ in brain *in vivo*; reduced levels of APP in cell cultures		[28]
	Hippocampal rat neurons; APP/PSEN1 mutant mice; Aβ oligomer-induced toxicity in nonhuman primates	Neurons: prevented Aβ oligomer-induced increase in IRS-1pSer, improving impaired axonal transport; Tg mice: reduced brain levels of IRS-1pSer636, IRS-1pSer312, and pJNK, with an improvement in cognition		[201]
Liraglutide	T2DM mice	Reversed DM-induced brain and peripheral insulin sensitivity, halted tau hyperphosphorylation	Randomised, placebo-controlled Phase II trial assessing safety and efficacy of liraglutide in 206 patients with early AD (NCT018430755) is underway; trial assessing effects of liraglutide on cerebral amyloid deposits (NCT01469351) is underway; pilot trial of liraglutide in patients with DLB is in planning stages	[114]
	ICV-STZ mice	Decreased hyperphosphorylation of tau and neurofilament proteins; improved learning and memory ability		[250]
	Senescence-accelerated mouse prone 8 (SAMP8) mice	Delayed progressive decline in memory function; increased memory retention and total hippocampal CA1 pyramidal neurons		[139]
	Db/db mice	Prevented hyperphosphorylation of tau protein in hippocampus		[113]
	7-month-old APP/PSEN1 mice	Prevented memory impairments in object recognition and water maze tasks; reduced synapse loss; reduced amyloid and dense core plaque load; reduced microglial activation		[61]
	Aβ oligomer-induced toxicity in rats	Improved spatial learning and memory water maze tests; improved LTP in hippocampal CA1 region		[26]
		Decreased levels of IRS-1pS616; reduced microglial activation; decreased amyloid plaque load		[202]
	14-month-old APP/PSEN1 mice	Improved spatial memory; reduced total brain APP and Aβ levels; increased IDE levels; increased neuronal progenitor cells and/or synapses in dentate gyrus		[251]
	2-month-old APP/PSEN1 mice	Prophylactic treatment improved memory formation in Morris water maze; prevented synapse loss; reduced amyloid plaque load, including dense core congophilic plaques; reduced activated microglia; enhanced neurogenesis in dentate gyrus		[252]
Lixisenatide	APP/PSEN1 mice	Increased LTP; prevented synapse loss; reduced amyloid plaque load; reduced microglial activation		[253]
	Aβ oligomer-induced toxicity in rats	Prevented Aβ-induced decline in spatial learning; improved LTP		[252]
DPP-IV inhibitor				
Saxagliptin	ICV-STZ mice	Halted Aβ, tau phosphorylation; reduced inflammatory markers; elevated hippocampal GLP-1; improved memory retention		[32]
Vildagliptin	ICV-STZ mice	Improved memory retention and dose-dependent attenuation of Aβ, tau phosphorylation, and inflammatory markers; elevated GLP-1 levels		[111]

TABLE 2 (*Continued*)

Drug	Experimental model	Results and/or effects	Human data	Refs
Sitagliptin	7-month-old APP/PSEN1 mice	Improved memory impairment in contextual fear conditioning test; increased brain levels of GLP-1; reduced inflammation markers; reduced APP and Aβ deposits		[33]
	OLETF T2DM rat model	Increased tau phosphorylation; increased IRS-1sP616		[34]
	Sprague-Dawley rats	Improved working memories; reduced insulin resistance; increased acetylcholine content of hypothalamus and Adipo R1 expression		[254]

growing evidence suggests that GLP-1 analogues and DPP-IV inhibitors modulate several events that are of relevance to the pathogenesis of PD (and AD).

Neuroinflammation

Inflammation is increasingly recognised as a key contributor to the pathogenesis of PD. Epidemiological studies suggest nonsteroidal anti-inflammatory drug (NSAID) use confers a decreased risk of developing PD [37]; positron emission tomography (PET) imaging of patients with early-stage PD showed significantly increased microglial activation [38], which could drive neuronal loss in both PDD and AD [39]; sustained expression of the proinflammatory cytokine tumour necrosis factor alpha (TNF-α) is associated with neurodegeneration of dopaminergic neurons [40]; and increased proinflammatory mediators are seen in the substantia nigra on postmortem examination [41]. Moreover, genome-wide association studies (GWAS) have reported an association between certain human leucocyte anagen (HLA) alleles and the risk of PD.

GLP-1 analogues and DPP-IV inhibitors have demonstrated anti-inflammatory properties across a range of experimental models of PD. Saxagliptin treatment in a rat rotenone model supressed production of TNF-α, inducible nitric oxide synthase (iNOS), and myeloperoxidase (MPO) [23]. Similarly, administering exendin-4 to rodents following nigrostriatal lesions induced by LPS and MPTP toxins prevented toxin-induced microglial activation and suppressed production of proinflammatory cytokines, including TNF-α and interleukin (IL)-1B. This was associated with restoration of extracellular DA and tyrosine hydroxylase (TH) activity, with subsequent motor and behavioural improvements [17,20]. More recently, in diabetic rat models, exenatide and liraglutide treatment had antipsychotic, anxiolytic, and antidepressant effects [42–44], which have been speculated to be due, in part, to its anti-inflammatory effects [45].

Regulation of microglial activity is thought to have a critical role in neuroinflammation in PD. While microglial activation might initially be protective in the initial stages, prolonged activation by alpha-synuclein, proinflammatory cytokines, and neighbouring neuronal death [46–49] can lead to polarisation towards the cytotoxic M1 phenotype. This can be severely damaging as the disease progresses [50], leading to a continuous and self-perpetuating persistent inflammatory environment [51,52], and has been identified as a major factor in driving dopaminergic degeneration in PD [39]. Correspondingly, strategies to enhance the cytoprotective M2 microglial response in models of PD have proven to be neuroprotective [53,54], highlighting the importance of microglia regulation.

The ability of GLP-1 analogues to suppress cytotoxic microglial responses and enhance cytoprotective phenotypes have demonstrated benefits across a variety of experimental models. GLP-1-mediated inhibitory effects on microglia have resulted in: reduced infarct size and neuronal death in models of stroke [55–59]; reversal of cognitive and behavioural impairments in rodent models of traumatic brain injury (TBI) [60–62]; prevention of hippocampal synapse loss in (APP)/presenilin-1 (PSEN1) and intracerebroventricular (ICV) streptozotocin (STZ) rodent models of AD [63,64]; reduced circulating monocyte cytokine production and psoriatic plaque severity in patients with diabetes and psoriasis [65], and attenuation of atherosclerotic lesions in arterial walls in models of myocardial ischaemia/reperfusion injury (reducing monocyte and/or macrophage accumulation) [66,67].

The underlying mechanism responsible for GLP-1 analogues modulation of microglial function remains under debate, but might involve regulation of the transcription factor nuclear factor (NF)-κB, an important downstream target of the GLP-1R/PI3K/AKT pathway, which regulates inflammatory gene expression and mediates the proinflammatory response of microglial cells. Perhaps not unsurprisingly, NF-κB has also been implicated in the pathogenesis of PD. Increased NF-κB activity is seen in TH+ dopaminergic neurons and in astrocytes and microglia in the substantia nigra pars compacta (SNPc) of patients with PD and in animal models [68]. By contrast, inhibition of NF-κB is neuroprotective in models of PD [69,70] and retards ageing and increases lifespan in mice [71]. Saxagliptin and vildagliptin have both been shown to significantly suppress NF-κB expression (and subsequent proinflammatory cytokine cascades) in a rotenone rodent model of PD [23,72]. Similarly, exendin-4 administration has been shown to inhibit activation of NF-κB and the resultant inflammatory response in endothelial cells [73], rodent models of obesity [73,74], and renal injury [75,76], resulting in improved cell survival. Although extensive crosstalk exists because various proinflammatory mediators can directly activate NF-κB [77], upregulation of the AKT pathway also upregulates IκBα, a specific endogenous inhibitor of NF-κB, resulting in reduced neuroinflammation [78], suggesting a possible mechanism linking GLP-1R activation and inflammation.

Mitochondrial function and/or oxidative stress

As regulators of cellular energy homeostasis and cell death signalling, the continued integrity of mitochondria within a cell is crucial for its sustained health. In particular, dopaminergic neurons of the SNPc have characteristically long-range projections that require a high rate of mitochondrial oxidative metabolism

and, therefore, are vulnerable to events that interfere with mitochondrial function. In parallel, significant evidence suggests that events that affect mitochondrial function, such as defective mitophagy, increased accumulation of mtDNA mutations, defects of complex I of the respiratory chain, accumulation of alpha-synuclein, dysregulated mitochondrial calcium homeostasis, and increased oxidative stress, are all involved in the pathogenesis of PD and, furthermore, can promote further injury to neighbouring mitochondria, creating a vicious cycle of further degeneration [79,80].

GLP-1R activation has demonstrated multiple beneficial actions on mitochondria across a range of experimental models. Saxagliptin preserved mitochondrial function by elevating complex I and antiapoptotic protein B-cell lymphoma 2 (Bcl-2) in a rat rotenone model of PD [23] and geniposide, a novel GLP-1 agonist, upregulated expression of Bcl-2 with subsequent reduced caspase 3 activation, resulting in preservation of dopaminergic neurons in an MPTP mouse model of PD [81]. Similarly, exendin-4 has been shown to increase mitochondrial biogenesis, number, and mass in rat insulinoma cells [82], and to inhibit the mitochondrial apoptotic pathway, resulting in functional improvements in rat models of spinal cord injury [83] and protection of retinal cells in diabetic rats [84]. In addition, exenatide was able to improve mitochondrial respiration and suppress the opening of the mitochondrial permeability transition pore, resulting in attenuation of myocardial hypertrophy and oxidative stress-induced injury in rodent models of myocardial ischaemia, leading to increased survival rates [85].

Recent studies have suggested how GLP-1R activation influences mitochondrial function. In a mouse model of amyotrophic lateral sclerosis (ALS), the neuroprotective effects of exendin-4 treatment were associated with modulation of mitochondrial intracellular calcium [86] and increased expression of mitofusin-2 (Mfn2), an endoplasmic reticulum (ER)–mitochondria-tethering protein that enhances ER–mitochondria coupling [87,88]. This is particularly relevant because a recent study suggested that alpha-synuclein causes mitochondrial fragmentation and/or damage by reducing this ER–mitochondrial connectivity [89].

Growing evidence also implicates the PI3K/AKT pathway as being partly responsible for the effects of GLP-1R activation on mitochondria [90]. Activation of GLP-1R causes upregulation of AKT, leading to inhibition of FOXO1 and reduced production of proapoptotic proteins (BiM and FAS), while concurrent GLP-1R-induced elevation of cAMP enhances upregulation of antiapoptotic proteins (Bcl-2 and Bcl-XL). Together, these actions contribute to preserving mitochondrial function by helping stabilise the outer mitochondrial membrane, preventing efflux of cytochrome *c* into the cytoplasm and reducing the activation of caspase 9 and 3, subsequently resulting in reduced apoptosis and oxidative stress [91–93].

In addition, a recent study highlighted another important pathway that might be involved in mitochondrial biogenesis. Exendin-4 administration in pancreatic β cells was associated with a twofold increase in the expression of peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC-1α) [82], a master regulator of mitochondrial biogenesis. Perhaps highlighting the importance of mitochondrial function in the pathogenesis of PD, growing evidence implicates dysregulated PGC-1a activity as playing a critical role in the pathogenesis of PD. GWAS studies revealed the downregulation of PGC-1α-responsive genes in patients with early PD [94]; PGC-1α polymorphisms are associated with increased risk of early-onset PD [95] and *in vitro* studies indicate that loss of PGC-1α is associated with increased accumulation of alpha-synuclein [96]. Conversely, overexpression or activation of PGC-1α protects dopaminergic neurons from MPTP-induced degeneration *in vivo*, enhances mitochondrial biogenesis, and prevents alpha-synuclein-induced dopaminergic neuronal loss [94].

Importantly, post-translational mechanisms, such as acetylation and protein phosphorylation, can regulate the activity of PGC-1α (and hence mitochondrial biogenesis), and can be influenced by genetic and environmental factors.

GLP-1 analogues have not been shown to interact with PGC-1α directly, but studies suggest that GLP-1R activation can influence PGC-1α activity indirectly. In models of liver disease, exendin-4 treatment led to upregulation of Sirtuin 1 (SIRT1; an NAD-dependent protein deacetylase and known upstream regulator of PGC-1α activation) [97,98], which, together with AMPK activation, resulted in enhanced PGC-1α activity, improvements in mitochondrial function, and reduction in ER stress and inflammation [99,100]. Similar results demonstrated in models of CNS disease suggest that GLP-1 analogues also modulate the expression of SIRT1 in neurons. In mice fed a high-fat diet, liraglutide decreased oxidative stress and inflammation, which was associated with increased expression of SIRT1 [101]. Encouragingly, studies indicate that SIRT1 overexpression is protective in many cell and animal models of PD [102]. Similarly, regular exercise, known to reduce the risk of PD and improve function outcomes in patients with PD, induces upregulation of SIRT1 and, as a result, increases PGC-1α activity. In addition, resveratrol, a potent activator of SIRT1, protects against 3-nitropropanoic acid (3-NP)-induced motor and behavioural deficits and improved motor function in mice via increased PGC-1α activity and increased mitochondrial biogenesis [103,104]. Taken together, there is accumulating evidence linking GLP-1R activation and mitochondrial function.

Protein aggregation

Dysfunction of lysosomal systems, disruption of normal processes through which cells degrade abnormal proteins and/or cellular constituents (autophagy), and the aggregation of alpha-synuclein into toxic fibrils, are thought to be crucial steps in the process leading to the degeneration of dopaminergic neurons in PD, and are also implicated in PDD and Dementia with Lewy bodies (DLB). Recent studies indicate that 50% of patients with PDD also have Aβ plaques and hyperphosphorylated tau-containing neurofibrillary tangles, which are usually seen in the brains of patients with AD. Furthermore, Aβ is an independent predictor of cognitive decline in PD [105] and this co-morbid pathology might act synergistically with Lewy bodies and Lewy neurites to lead to toxic gain of function and confer a worse prognosis [106–109]. This has led some to suggest that agents that can influence the development of AD-related pathology would be beneficial in a subset of patients with PDD.

In vitro studies show that GLP-1 analogues can alter the cellular production and accumulation of Aβ deposits, reduce Aβ-induced cell death and toxicity and levels of amyloid precursor protein

(APP) [30,110], and decrease levels of secreted Aβ in human neuroblastoma cultures [111]. Similarly, *in vivo* treatment with the GLP-1 analogues exenatide, liraglutide and lixisenatide has been shown to reduce tau hyperphosphorylation [112,113], amyloid plaque load, and soluble Aβ levels across a range of models of AD, counteracting their toxic effects and leading to improvements in memory performance and learning. Data regarding the effects of DPP-IV inhibitors on AD-related pathology are conflicting: while saxagliptin, vildagliptin, and sitagliptin were shown to reduce tau and Aβ deposits in ICV STZ and APP/PSEN1 mice models of AD [34,35,114], in a Otsuka Long-Evans Tokushima fatty (OLETF) T2DM rat model, sitagliptin paradoxically increased tau phosphorylation, although differences in methodology might account for these observations [36].

Studies indicate that the effects of GLP-1 analogues on amyloid aggregation are at least partially due to activation of the PI3K/AKT pathway, resulting in increased phosphorylation (and inactivation) of downstream target Glycogen synthase kinase 3 beta (GSK-3B) [115–117]. GSK-3B is a major kinase involved in promoting phosphorylation of tau and aggregation of Aβ through modulation of APP processing [118] and, correspondingly, inhibition of GSK-3B activity has been linked with neuroprotection and reduced AD pathology. GSK-3B is also involved in modulating autophagy, and dysregulated GSK-3B activity is implicated in PD pathogenesis and promotion of Lewy body formation [119]. Correspondingly, studies demonstrate that inhibition of GSK-3B can promote autophagy and halt the expression and aggregation of alpha-synuclein and its subsequent neurotoxic effects *in vitro* and *in vivo* [120,121].

GLP-1R activation-induced upregulation of SIRT1 in neurons might also contribute to beneficial effects on protein aggregation [101]. As well as influencing mitochondrial function via modulation of PGC-1α, SIRT1 is also involved in the regulation of autophagy. In models of PD, increased expression of SIRT1 activated heat shock protein 70 (Hsp70), a molecular chaperone that promotes normal folding of alpha-synuclein. Furthermore, in models of AD, SIRT1 reduced plaque formation by activation of retinoic acid receptor β, which activates ADAM10 to facilitate processing of APP along a nonamyloidogenic pathway, and can directly deacetylate tau, enabling ubiquitin ligases to promote its clearance [102,122,123]. Correspondingly, in experimental models of PD and AD, compounds that increase SIRT1 expression can reduce alpha-synuclein aggregation, and Aβ and neurofibrillary tau pathology, respectively, resulting in improved behaviour [102].

Recently, geniposide was shown to upregulate expression of insulin-degrading enzyme (IDE), a zinc-metalloendopeptidase that can degrade insulin and other small peptides that can form β-pleated sheets. IDE is activated by PI3K and was recently shown to inhibit alpha-synuclein fibril formation *in vitro* by binding to alpha-synuclein oligomers, blocking them from forming fibres [127]. IDE can also bind and degrade Aβ, halting their neurotoxic toxic effects [128–130], and recent studies showed that upregulation of IDE by geniposide antagonised cell damage induced by Aβ1–42 exposure in primary cultured cortical neurons [124] and reduced Aβ1–42 levels in diabetic rats [125] (reviewed in [126]).

A recent study also showed that, via an increase in cAMP response element-binding protein (CREB; a downstream effector of the PI3K/AKT pathway), exendin-4 caused upregulation of ADAM10 at the plasma membrane in adult mice, which promoted a nonamyloidogenic APP-processing pathway, potentially representing another mechanism responsible for reducing levels of Aβ *in vivo* [131].

Neurogenesis

Neurogenesis continues to occur throughout adulthood in the subgranular zone of the dentate gyrus in the hippocampus and the subventricular zone (SVZ) near the lateral ventricle, although its levels decline with age. These endogenous stem cells can migrate into the granule cell layer of the dentate gyrus, develop neuronal markers, and eventually become integrated within local circuits [132]. In particular, it is thought that the SVZ continually provides GABA- and DA-containing interneurons for the olfactory bulb. However, postmortem studies suggest that the age-related decline in adult neurogenesis is accelerated in patients with PD [133,134], possibly due to dopaminergic depletion having a negative effect on cellular proliferation [135,136]. Although the relations are not entirely understood, altered neurogenesis in the hippocampus in PD [133] might be linked with impairments not only in memory processing, but also in olfaction and depression [135,137].

GLP-1R are expressed in the hippocampus and SVZ and exendin-4 treatment has been shown not only to stimulate cellular proliferation in human neuronal cell cultures [138–140], but to also promote differentiation into more mature neuronal phenotypes [19,111,138,141]. In experimental models of PD, exendin-4 treatment 1 week after 6-OHDA-induced nigrostriatal degeneration stimulated neurogenesis in the SVZ of the rat brain and improved dopaminergic markers, leading to functional motor improvements and normalisation of behaviour [19]. Similarly, chronic treatment of rodents with exendin-4 enhanced hippocampal neurogenesis and led to improvements in reference memory performance and decreased immobility in the forced swim test, suggesting improvements in cognitive function and mood disorders [141]. In both studies, these effects persisted weeks after cessation of treatment, or became apparent only after chronic administration, suggesting possible neuroregenerative effects. However, it is unclear whether the reduced TH+ staining seen in the striatum following initial neurotoxin administration in these models represents a phenotypical shift in protein expression rather than cell loss, and whether exendin-4 is able to 'restore' the phenotypic expression as a result of trophic effects rather than to stimulate the generation of new neurons. In addition, improvements in cognitive performance following liraglutide administration in rodent models of AD were associated with increases in hippocampal CA1 neuronal numbers [32,142–144].

How GLP-1R activation influences neurogenesis is unclear, but studies indicate that activation of the PI3K/AKT pathway is needed for many of the effects on cellular proliferation and differentiation [145–148]. Recent studies showed that liraglutide-induced hippocampal neurogenesis is accompanied by increased expression of Mash1, an important regulator of neuronal precursor production [142,149] that is required for AKT-induced neuronal differentiation [150]. However, because neurogenesis can be stimulated by diverse factors, such as exercise [151], antidepressants [152], and neurotrophic factors [153], and is also decreased by ageing, insulin resistance [154], microglial activation [155], loss of DA neurons [156], and aggregation of alpha-synuclein [135], it might be reasonable to suggest that activation of GLP-1R indirectly influences

neurogenesis through limiting effects on other pathogenic processes. For example, the inhibitory effects of exendin-4 on microglial activation were associated with increased stem and/or progenitor cell proliferation in the SVZ and neuroblast production in the striatum in a rodent model of stroke [59].

Trophic factors

Trophic factors can influence cell survival and axonal growth and have the potential to protect degenerating DA neurons as well as to promote regeneration of the nigrostriatal DA system [157]. Therefore, the exogenous administration of neurotrophic factors to the PD midbrain and/or striatum to slow or halt degeneration of dopaminergic neurons has become a promising active area of research. However, despite the potential of this method, current studies have been hampered by the inherent poor ability of trophic factors to cross the BBB, leading to alternative methods of administration using viral vectors [158] or intranasal delivery [159] being explored.

Despite their large molecular size, peripherally administered GLP-1 analogues can cross the BBB to facilitate trophic factor expression. Brain-derived neurotrophic factor (BDNF), a trophic factor that can rescue dopaminergic neurons, reverse synapse loss after disease onset [160], and promote neural progenitor cell differentiation and survival, was shown to be upregulated by intraperitoneal exendin-4 administration in adult mice [131]. Similarly, the neuroprotective effects of saxagliptin in a rotenone model of PD were accompanied by an increase in striatal BDNF [23].

Studies show that GLP-1 analogues might also directly act as a neurotrophic factor. In PC12 cells, exendin-4 exposure induced neurite outgrowth in a manner similar to nerve growth factor (NGF) [138,161] and, furthermore, these effects on neurite outgrowth translated to functional improvements in sensory electrophysiology and behavioural sensory loss in models of diabetic polyneuropathy [162,163]. Importantly, these studies showed that GLP-1R activation was able to rescue degenerating cells after NGF-mediated withdrawal, suggesting independent trophic effects [164,165]. Furthermore, in different tissue models, pretreatment with exendin-4 improved the survival, adhesion, and therapeutic efficacy of transplanted adipose-derived stem cells (ADSCs) in ischaemic myocardium [166–168] and islet cell transplants [169].

These trophic effects might be mediated by activation of the AKT pathway and increases in intracellular cAMP, given that BDNF is a transcriptional target of cAMP response element-binding protein (CREB), which are both elevated in response to GLP-1R activation. Similar effects on neurite outgrowth effects are thought to be mediated via the rise in intracellular cAMP and induction of the MAPK/ERK pathway, which promotes neuronal survival in response to nutrient depletion [161,170].

Learning and memory

The clinical phenotype of PD evolves due not only to neurodegeneration, but also to abnormal patterns of firing of interconnected neuronal pathways. Dysfunctional synaptic plasticity has been implicated in the initial onset of PD [171,172], has relevance in the development of the motor complications of PD, such as dyskinesias [172,173], and also might partially contribute to the complex evolution of cognitive impairment. Dementia is common in the advanced stages of PD, affecting up to 80% of patients [174], and often heralds impending residential care and mortality; however, mild cognitive impairment (MCI) can occur in early stages and a quarter of patients already have evidence of cognitive deficits at diagnosis [175,176].

Given its role as an integrator of memory formation, alterations in hippocampal structure and function are implicated in cognitive decline in PD [177,178], correlate with memory defects and behavioural abnormalities [178,179], and might predict progression to PDD [180]. GLP-1R-activated signalling appears to be involved in memory. GLP-1Rs are present in the CA2–CA3 region of the hippocampus in abundance [181] and studies have shown that mice lacking GLP-1R have learning deficits and their neurons display impaired LTP (the cellular correlate of memory formation) [182]. Conversely, GLP-1 analogue administration in rodents and rats overexpressing GLP-1R demonstrate improved hippocampal CA1 LTP and synaptic plasticity, resulting in subsequent improved spatial learning and memory performance [26,144,183], effects that were blocked in the presence of a GLP-1R antagonist.

Significant evidence also implicates the cholinergic system arising from the substantia innominate of the basal forebrain as having a key role in cognitive decline in PD. Imaging combining PET with *N*-[^{11}C]-methyl-4-piperidyl acetate (MP4A) and 18F-fluorodopa (FDOPA) showed severe cholinergic deficit in temporal and parietal regions in patients with PDD compared with patients with PD [184]. In addition, postmortem studies showed that patients with PDD and AD had lost >90% of neurons in the nucleus basalis of Meynert (NBM) compared with age-matched controls, resulting in a cortical cholinergic deficit [185,186]. More recent *in vivo* studies using PET and volumetric magnetic resonance imaging (MRI) confirmed that this cortical cholinergic deficit is greater in patients with PDD (or AD) compared with controls [187], and correlates to the degree of cognitive impairment [188,189]. Whereas augmentation of these neurotransmitter deficits with rivastigmine, an acetylcholinesterase inhibitor (and the only licensed treatment for PDD and DLB), has positive effects on cognition and behavioural disturbance, it can often worsen motor deficits [190].

GLP-1 analogues can improve the functionality of cholinergic neurons; exendin-4 was shown to enhance acetylcholine production [identified through elevated choline acetyltransferase (ChAT) activity] in NSC19 cells [165]. Furthermore, in studies using ChAT-positive immunoreactivity as a marker for cholinergic cell bodies *in vivo*, exendin-4 significantly reduced ibotenic acid-induced loss of cell bodies in NBM cholinergic neurons within the basal forebrain in a rat compared with controls, demonstrating its ability to restore cholinergic marker function following excitotoxic damage [164].

In conclusion, activation of GLP-1R via GLP-1 analogues or indirectly via DPP-IV inhibition has a remarkable array of protective effects on cellular proliferation, differentiation, inflammation, and mitochondrial function, and also might be associated with reduced levels of alpha-synuclein and amyloid plaques in the brain.

Insulin resistance

A growing body of data suggests that T2DM and PD share common pathological mechanisms. Epidemiological studies suggest that

T2DM increases the risk of developing PD by 40%, whereas peripheral insulin resistance, broadly defined as reduced tissue responsiveness to insulin, is associated with a more severe clinical phenotype, accelerated disease progression, and increased risk of cognitive decline [191]. Furthermore, studies indicate that a process analogous to peripheral insulin resistance occurs in the brains of patients with PD and might be responsible for initiating and/or exacerbating neurodegeneration (F. Bassil, unpublished data, 2015) [192–195].

Within the CNS, although not directly involved in glucose uptake, insulin is able to modulate many processes disrupted in PD, including apoptosis, autophagy, mitochondrial biogenesis, oxidative stress, neuroinflammation, protein synthesis, alpha-synuclein aggregation, and synaptic plasticity [80,196]. These effects are mainly via activation of two pathways (MAPK/ERK and PI3K/AKT) and, accordingly, experimental models of insulin resistance demonstrate enhanced nigrostriatal neurodegeneration, accelerated microglia cell activation, and alpha-synuclein aggregation in both pancreas and midbrain [197] and altered DA turnover resulting in enhanced motor deficits, impaired cognition, and behavioural disorders compared with matched controls [198–201].

The relation between insulin resistance and neurodegeneration is not limited to PD, and similar links exist in AD, where studies suggest prolonged metabolic stress and Aβ induce production of proinflammatory cytokines that can phosphorylate and activate insulin receptor substrate 1 (IRS-1) serine kinases IκB kinase (IKK), Janus kinase (JNK), and Erk2. In turn, these kinases ultimately phosphorylate IRS-1 at serine residues, causing inactivation and inhibition of downstream insulin signalling [202–205].

Although the cause of insulin resistance in PD is still be elucidated, recent studies suggest that alpha-synuclein negatively regulates insulin signalling in a similar manner. Either through inhibition of protein phosphatase (PP)2A activity, sustaining mTORC1 activation, enhancing an insulin-signalling negative feedback loop, and increasing degradation of IRS-1 [206] or via alpha-synuclein-induced microglial production of proinflammatory cytokines, leading to activation of IKK or JNK, and ultimately phosphorylation and inactivation of IRS-1 at serine residues, thereby sustaining a vicious cycle of aggregation and neurodegeneration.

Consequently, because GLP-1R stimulation activates similar pathways 'de-activated' as a consequence of insulin resistance, some have suggested that it is the ability to restore brain insulin sensitivity that is responsible for the diverse range of its pleotropic effects. Exenatide and liraglutide have been shown to reduce levels of IRS-1pS616 and IRS-1pS36 (putative biomarkers of neuronal insulin resistance in AD) in the APP/PSEN1 model of AD and diabetic mice, leading not only to facilitation of insulin signalling, but also the restoration of normal tissue responses to insulin [116,207,208], resulting in improvements in AD pathology and functional improvements in cognition. Similarly, a novel GLP-1R agonist, geniposide, attenuated insulin deficiency-induced Aβ accumulation in a APP/PSEN1 Tg model of AD [209].

GLP-1Rs are also ubiquitously distributed throughout the body and, as such, GLP-1R stimulation has an array of systemic effects that might also be of relevance in regards to limiting neurodegeneration based on reducing insulin resistance. Ageing, obesity (or rather increased adiposity), and metabolic stress (such as peripheral insulin resistance) are risk factors for PD and contribute to a state of chronic systemic inflammation [198]. Furthermore, studies indicate that proinflammatory cytokines can cross the BBB to directly induce cell death and/or activate IRS serine kinases, such as JNK, in a similar manner to activated microglia to induce and/or exacerbate neuronal insulin resistance [210,211].

Weight loss is an effective method in reducing the development of peripheral insulin resistance and GLP-1 analogues have long-lasting anorexic effects. The mechanism is uncertain but might involve increasing energy expenditure [212–214], reducing gastric emptying, decreasing nutrient absorption, inducing nausea, or promoting satiety through stimulation of hypocretin and/or orexin neurons in the lateral hypothalamus [213,215,216], which ultimately can result in reduced levels of systemic inflammatory markers (as observed in patients with psoriasis) [65].

As well as driving systemic inflammation, excessive peripheral adipose tissue can alter lipid composition and function of hippocampal synapses [217]. GLP-1 analogues can improve insulin sensitivity in obese mouse models by directly inhibiting inflammatory pathways in adipocytes and, via upregulation of the transcription factor peroxisome proliferator-activated receptor gamma (PPAR-y), can regulate adipogenesis, promoting preadipocyte proliferation, which reduces apoptosis [74,218,219]. Dysregulation of ceramides (lipids derived from fatty acid metabolism) is altered in patients with PD and is associated with worse cognition [220,221]. Studies show that they can cross the BBB to activate microglia, inducing central inflammation and cell death [222], and also directly inhibit central insulin signalling leading to enhanced nigrostriatal degeneration [223]. In addition alterations in their metabolism are associated with the misfolding and aggregation of alpha-synuclein [224]. Nonalcoholic steatohepatitis (NASH) occurs frequently with T2DM and obesity, contributes to peripheral insulin resistance, and, via increased endogenous hepatic TNF-α expression, can increase the production of peripheral ceramides in adipose tissue. This has been shown to contribute to CNS oxidative stress, insulin resistance, and neuronal cytoskeletal collapse [223]. Recent studies have shown that exenatide reversed hepatosteatosis-induced cognitive and behavioural deficits in rats, which were accompanied by reduced levels of brain TNF-α [225]. These effects were thought to be mediated by increased expression of SIRT1 and activation of the AMPK pathway, leading to beneficial effects on mitochondrial function, reduction in ER stress, and reduced lipogenesis, fat storage, and inflammation [99,100].

Taken together, due to the distribution of GLP-1Rs, stimulation with analogues or indirectly with DPP-IV inhibitors can lead to wide-ranging systemic effects on whole-body metabolism, improving peripheral and central insulin resistance.

The AKT pathway

Studies have implicated the involvement of PI3K/ERK/MAPK and PI3K/AKT-dependent pathways as being important in GLP-1R activation in terms of diverting signalling away from apoptosis towards cell survival. Although it difficult to separate the relative contribution of each pathway because extensive crosstalk exists, some studies that utilise selective AKT inhibitors suggest that the AKT pathway is at least partially responsible for the effects of GLP-1R stimulation on cellular proliferation [226], trophic effects [90], and antiapoptotic effects [227,228].

Able to phosphorylate over 50 downstream protein substrates, AKT acts as a master regulator of cellular function [229]. The AKT pathway has been identified as a central hub that might be responsible for degenerating dopaminergic neurons in PD [230,231] and some important downstream effectors, such as GSK-3B, mTOR, caspase-9, and the transcription factor FOXO1, have themselves been identified as novel targets for halting neurodegeneration in PD. Substantial evidence suggests that loss of control of AKT signalling is involved in several age-related diseases, including AD [232], and growing evidence suggests that altered AKT signalling is also a key component of PD pathogenesis and influences alpha-synuclein aggregation [233], providing a possible link between insulin resistance and neurodegeneration in PD [229,230,233–237]. In parallel, studies using trophic factors or small molecules to activate AKT appear to slow neurodegeneration in PD [238–240]. However, as with any biological system, negative feedback control of AKT is essential to maintain optimal tissue function; for example, although AKT usually inactivates FOXO, physiological FOXO activity is a critical counterbalance to allow necessary transcription of stress-response genes and repair systems [241,242], and studies show that elevated AKT phosphorylation is associated with levodopa (L-DOPA)-induced dyskinesias in MPTP-treated monkeys [243].

Thus, the protective effects of restoration of insulin signalling might be due, in part, to an increase in the basal activation of the AKT pathway, restoring the balance and activating signalling cascades that ultimately promote cellular survival.

The therapeutic potential of GLP-1R activation

In regards to their potential utility in PD, GLP-1 analogues and DPP-IV are emerging as promising therapeutic agents in PD, regardless of whether their useful mechanisms of action in neurodegeneration are via an insulinotrophic effect, an effect on IRS-1 phosphorylation, or GLP-1 receptor action on AKT. However, maximising the translational potential of this approach is crucial, and significant differences regarding their pharmacodynamics and pharmacokinetic properties exist between not only the drug classes, but also compounds of the same class, which is reflected in variations in their efficacy in glycaemic control in diabetes. Thus, it might be reasonable to assume that some might exert greater neuroprotective effects in PD than others, although current comparable data in PD are sparse. Studies from diabetic populations suggest that the risk of inducing hypoglycaemia with either GLP-1 analogues or DPP-IV inhibitors in a nondiabetic population is low; however, weight loss and gastrointestinal adverse effects are less common with DPP-IV inhibitors than with GLP-1 analogues [244], which is potentially significant if utilising these drugs in older, often frail, populations.

Although no clinical data yet exist, extrapolating the more positive results of DPP-IV inhibition seen in animal models to humans might be difficult: doses of DPP-IV inhibitors used in these animal models are 10–20 times higher than those used in T2DM and, as such, the high levels of brain GLP-1 in rats produced by DPP-IV inhibition might be difficult to reproduce in humans. Similarly, DPP-IV inhibitors have low penetration of the BBB. Conversely, GLP-1 analogues, with the exception of dulaglutide, are all able to penetrate the BBB to some degree in experimental models [15,16] and exert central effects in doses comparable to those in humans [9].

Similarly, data regarding the comparison between individual GLP-1 analogues in models of PD are limited. Data from diabetic studies suggest that liraglutide is associated with greater effects on glucose homeostasis than exenatide, but has greater incidence of adverse gastrointestinal effects [245], whereas exenatide has been linked to a small increased risk of pancreatitis in patients with diabetes (although subsequent meta-analysis has not supported this link). Few studies have attempted to compare the effects of GLP-1 analogues in models of PD: a recent study indicated that, in comparison to liraglutide and lixisenatide, exenatide was unable to offer protection against MPTP-induced dopaminergic degeneration in a mouse model [22] (which could be explained by differences in equivalent dosing). Similarly, in mice, whereas liraglutide and lixisenatide were both able to cross the BBB and enhance neurogenesis in the dentate gyrus, lixisenatide achieved significantly higher increases in cAMP compared with liraglutide, and at lower doses [16].

Data regarding GLP-1 analogues and/or DPP-IV inhibitor use in clinical trials of PD are limited but encouragingly: exenatide exposure in a small, open-label randomised controlled trial in 45 patients with PD led to a mean advantage of 7.0 points on the MDS-UPDRS Part III, which persisted after a 12-month 'wash-out' period, together with improvements in the Mattis Dementia Rating scale and well as other non-motor areas [246,247]. The single-blind design of this trial does not yet confirm proof of efficacy, but the encouraging results have prompted conduct of a larger, double-blind trial using a once-weekly, long-acting form of exenatide in moderate-stage PD, with results expected in May 2016 (Clinicaltrials.gov identifier NCT01971242).

In parallel, encouraging results from an double-blind randomised controlled trial assessing the effects of liraglutide on cerebral amyloid deposits in patients with AD have recently been reported, suggesting that liraglutide treatment halted decline of the cerebral glucose metabolism compared with controls. This hints at an ability of liraglutide to stabilise energy metabolism in areas of the brain that have been shown to correlate with cognitive decline in patients with AD [248]. Similar trials evaluating GLP-1 analogues in AD are ongoing: a Phase II trial evaluating exenatide in 230 patients with AD or MCI (NCT01255163) is currently underway and a randomised placebo-controlled Phase II trial assessing the safety and efficacy of liraglutide in 206 patients with early AD (NCT018430755) is continuing.

In terms of future directions, although the current crop of GLP-1 analogues (exenatide, liraglutide, and lixisenatide) are effective in reducing insulin resistance, newer molecules, such as unimolecular dual GLP-1/glucose-dependent insulinotrophic polypeptide (GIP) agonists or triple GLP-1/GIP/glucagon receptor agonists, have been shown to have superior efficacy in reducing peripheral insulin resistance compared with conventional 'mono' GLP-1 agonists [249,250] with additional benefits of reduction of adverse gastrointestinal effects. A novel dual GLP-1/GIP receptor agonist was recently shown to attenuate dopaminergic cell death in an MPTP mouse model of PD [251] and these newer agents might also deserve to have their potential effects explored in PD.

Concluding remarks

GLP-1R stimulation is associated with an impressive array of positive actions that are relevant to PD pathogenesis, such as enhancing mitochondrial biogenesis, suppressing microglial activation and inflammation, enhancing autophagy, and clearance of aggregated proteins, and it is probably that it is this combination of actions that accounts for its positive effects in models of not only PD, but also AD, Huntington's disease, TBI, and ALS.

Further research will clarify whether insulin resistance is a cause or consequence of neurodegeneration in PD, but, if confirmed, this might offer clinicians a useful window to try to identify high-risk individuals (e.g. those with metabolic syndrome or other genetic risk factors) and offer appropriate measures to slow this process (and thus neurodegeneration).

It is also becoming increasing clear that the pathophysiology of PD is not confined to a limited range of organs or cell systems, but is rather a system-wide disorder, with complex interplay between peripheral and central organs. This is supported by evidence of systemic dysregulated metabolism in patients often years before motor symptoms become apparent, which more importantly can impact the course of degeneration within the CNS, suggesting a common pathological signalling system and/or axis (such as a ligand–receptor axis) present centrally and peripherally, which, when disrupted by an initiating factor, leads to system-wide pathophysiological disruption. This implies that a suitable agent might be able to modulate and restore these dysregulated networks in a whole-body approach, which by its nature is more efficient and likely to be more successful than an agent specially targeting one aspect of the neurodegenerative pathway [252].

Given its expression in a variety of tissues throughout the body and involvement in mediating systemic and peripheral inflammation, metabolic homeostasis, gut–brain signalling, cardiovascular activity, and circadian rhythms [253], GLP-1/GLP1R has been proposed as a likely candidate for one of the ligand–receptor signalling axes exerting multiple effects in PD [252]. Therefore, GLP-1R activation by agonists could explain the range of systemic and neuroprotective effects of GLP-1 stimulation seen in models of PD.

In future, research is focus on developing nonpeptidergic ligands that can modify the activity of the GLP-1R itself, which, theoretically, would be able to exert more potent effects on GLP-1R at multiple levels, thus maximising their effects. Although some novel compounds have been developed with evidence of efficacy at increasing cAMP and insulin potentiation [254,255], further research will be needed to ascertain whether maximising exploitation of this newly discovered signalling axis would offer greater benefits in the treatment of neurodegenerative diseases.

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