Insulin resistance and Parkinson's disease: a new target for disease modification?

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Abstract

There is growing evidence that patients with Type 2 diabetes have an increased risk of developing Parkinson's disease and share similar dysregulated pathways suggesting common underlying pathological mechanisms. Historically insulin was thought solely to be a peripherally acting hormone responsible for glucose homeostasis and energy metabolism. However accumulating evidence indicates insulin can cross the blood-brain-barrier and influence a multitude of processes in the brain including regulating neuronal survival and growth, dopaminergic transmission, maintenance of synapses and pathways involved in cognition. In conjunction, there is growing evidence that a process analogous to peripheral insulin resistance occurs in the brains of Parkinson's disease patients, even in those without diabetes. This raises the possibility that defective insulin signalling pathways may contribute to the development of the pathological features of Parkinson's disease, and thereby suggests that the insulin signalling pathway may potentially be a novel target for disease modification. Given these growing links between PD and Type 2 diabetes it is perhaps not unsurprising that drugs used the treatment of T2DM are amongst the most promising treatments currently being prioritised for repositioning as possible novel treatments for PD and several clinical trials are under way. In this review, we will examine the underlying cellular links between insulin resistance and the pathogenesis of PD and then we will assess current and future pharmacological strategies being developed to restore neuronal insulin signalling as a potential strategy for slowing neurodegeneration in Parkinson's disease.

Contents

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and globally affects 1% of people over age 60 (de Lau and Breteler, 2006), with the risk increasing with age. The hallmark of this progressive disorder is loss of nigrostriatal dopaminergic neurons causing characteristic motor signs and symptoms of tremor, rigidity and bradykinesia. Accumulating evidence suggest the onset of PD can begin up to 20 years prior to appearance of the classical motor symptoms while imaging and pathological studies suggest nigrostriatal degeneration can be detected 5-10 years before this clinical milestone (Hilker et al., 2005; Tolosa et al., 2009). During this time, the clinicopathological correlate, or molecular prodrome is thought to pass through a number of stages leading ultimately to neurodegeneration (Schapira et al., 2014). The exact pathophysiological mechanisms underlying neurodegeneration in the PD brain remain uncertain; however significant evidence implicates mitochondrial dysfunction, inflammation, oxidative stress and dysfunction of autophagy systems as being central to PD pathogenesis. Although these pathways have separate divergent routes and multiple points of interconnection leading to cell damage, there are thought to be common points of convergence "upstream" of these deleterious effects, which may be amenable to intervention (Schapira and Tolosa, 2010). Despite the large number of compounds showing neuroprotective properties in in vitro or animal models of PD, none so far have convincingly been shown to have any effects on disease progression in clinical trials (Athauda and Foltynie, 2014).

A growing body of epidemiological and clinical data suggest that Parkinson's disease and Type 2 diabetes (T2DM), both age-related diseases, share these similar dysregulated pathways(Aviles-Olmos et al., 2013b; Santiago and Potashkin, 2014), suggesting common underlying pathological mechanisms. In its earliest stage, T2DM develops from insulin resistance (broadly defined as a tissue's reduced responsiveness to insulin), leading to a variety of detrimental effects on metabolism and inflammation. Accumulating evidence suggests that similar dysregulation of glucose and energy metabolism seems also to be an early event in the pathogenesis of sporadic PD (Dunn et al., 2014). While insulin is well recognised for its role in mediating peripheral

glucose homeostasis, within the central nervous system (CNS) insulin seems to have neuroprotective effects. Insulin receptors are found in the basal ganglia and substantia nigra and growing evidence is emerging that suggests insulin plays an essential role regulating neuronal survival and growth, dopaminergic transmission and maintenance of synapses (Bassil et al., 2014). In conjunction, there is growing evidence that a process analogous to peripheral insulin resistance occurs in the brains of PD patients, (even in those without diabetes), which suggests loss of insulin signalling may contribute to the development of pathological features of PD.

Alongside the motor deficits associated with PD, one of the most significant non-motor symptoms is the development of cognitive impairment and dementia. The appearance of these symptoms can exacerbate functional impairments caused by motor symptoms (Rosenthal et al., 2010) and confers increased mortality and morbidity (Levy et al., 2002). Although Parkinson's disease dementia (PDD) and Dementia with Lewy bodies (DLB) share similar clinical and pathological features (suggesting these conditions are on the same spectrum of Lewy body diseases), the precise neuropathophysiology underlying the development of cognitive impairment in PD remains unclear. Studies have indicated deposition of Lewy body-related pathology in neocortical and limbic areas to be one of the most significant factors in the development of PDD and DLB (see(Halliday et al., 2014) for review). However the involvement of cerebral amyloid angiopathy, argyrophilic grains and microvascular disease has also been implicated, though their relative contributions remain unclear. Further evidence indicates that 50% of patients with PDD also have evidence of amyloid- β-peptide (AB) plaques and hyperphosphorylated tau-containing neurofibrillary tangles, pathology usually seen in the brains of patients with Alzheimer's disease (AD) (Compta et al., 2014; Irwin et al., 2013). The relative contribution of this AD-type pathology in cognitive decline in PD is still debated but some studies indicate that this co-morbid pathology may act synergistically with Lewy bodies and Lewy Neurites and confer a worse prognosis (Compta et al., 2011; Jellinger et al., 2002; Kotzbauer et al., 2012; Masliah et al., 2001).

The emerging questions thus relate to the extent to which insulin resistance may act as a mediator of both motor and cognitive impairments in PD. In this review, we will therefore focus on the evidence linking insulin resistance and PD, firstly by presenting a brief overview of

epidemiological data linking insulin resistance to PD and secondly, by using evidence from experimental models, we will review the data supporting the premise that insulin and insulin resistance play a role in the neurodegenerative processes of PD. Growing evidence suggests that AD-related pathology is undoubtedly relevant for at least a subset of individuals with PDD due to either superimposed AD-type pathology, or because of an interaction between AB and the rate of progression of cortical Lewy body/alpha synuclein pathology. We will therefore also review this relevant evidence emerging from research into insulin resistance and the development of AD-related pathology.

Most importantly, there are a growing number of preclinical studies suggesting that modulating the insulin signalling pathway and restoring insulin sensitivity may potentially be a novel target for disease modification. Finally, therefore we discuss the current pharmacological strategies aiming to restore neuronal insulin signalling as a potential neuroprotective treatment in PD.

2. PD and Type 2 diabetes

2.1 Data from epidemiological studies

Early reports previously suggested that up to 50% - 80% of patients with PD have abnormal glucose tolerance when tested (Sandyk, 1993), however data from more contemporary prospective studies suggest the association is more modest with T2DM patients having approximately a 40% increased risk of developing PD(Driver et al., 2008; Hu et al., 2007; Xu et al., 2011). Case-control studies from China, Taiwan and Denmark also indicate that T2DM is a risk factor for developing PD in these populations(Schernhammer et al., 2011; Sun et al., 2012; Wahlqvist et al., 2012). Though the majority of studies support this association, it must be noted that some studies have found no association(Palacios et al., 2011; Savica et al., 2012), or an inverse association (D'Amelio et al., 2009; Lu et al., 2014). This discrepancy may be possibly explained by differences in methodology and residual confounders such as methods of PD diagnosis attainment, concomitant drugs and other co-morbid medical conditions often found in diabetic populations. A Finnish prospective cohort study involving 51,552 individuals did attempt to address these confounders and suggested that T2DM is associated with an increased risk of

PD independent of known modifying risk factors including body mass index, systolic blood pressure, total cholesterol, smoking, alcohol and coffee consumption (Hu et al. 2007), but further epidemiological studies that take these and other confounders into consideration are needed to clarify the links between T2DM and PD.

Additional studies have also suggested that even insulin resistance or ”pre-diabetes” in patients with PD seems to negatively impact the course of the disease. Insulin resistance has been associated with a more severe PD phenotype, accelerated disease progression, and increased risk of PD dementia (Bosco et al., 2012; Cereda et al., 2012; Kotagal et al., 2013). Together, these findings emphasise the potentially detrimental effects insulin resistance has on PD and have highlighted the need to better understand the cellular processes underlying this association.

2.2 Insulin signalling in the brain

Historically insulin was thought of primarily as a peripherally secreted hormone, regulating glucose homeostasis by stimulating glucose uptake in muscle and adipose tissue and inhibiting glucose production by the liver and fatty acid production by adipose tissues. However, it is now clear that insulin also acts as a key homeostatic factor in the brain, essential for maintaining its physiological functions. The source of insulin within the brain remains under debate. The majority is thought to derive from pancreatic B-cells (Havrankova et al., 1978b; Sankar et al., 2002), and transported in the CSF into the brain, or via direct diffusion across the area postrema (Sankar et al., 2002). However insulin and the closely related insulin-like growth factor 1 (IGF-1) are also produced by pyramidal neurons in the cortex, hippocampus and olfactory bulb(Devaskar et al., 1994; Kuwabara et al., 2011), where densities of the insulin receptor are high (Baskin et al., 1988; Havrankova et al., 1978a; Hill et al., 1986). Unlike peripheral tissue, in the CNS insulin has no direct influence on neuronal glucose uptake into cells (Hoyer et al., 1994), but plays a central role in modulating many functions in the brain and broadly speaking, through downstream effectors, promotes cell survival (Bassil et al., 2014).

A detailed description of insulin receptor signalling pathway will not be attempted here (see (Ghasemi et al., 2013) for review) but an overview of the pathways of relevance to PD will be described. Insulin binding to its receptor triggers tyrosine kinase activity, leading to phosphorylation of insulin receptor substrates (IRS) -1 and -2 on tyrosine residues which can then phosphorylate downstream effectors that activate secondary messenger pathways (Hotamisligil et al., 1996). IRS proteins essentially regulate insulin signalling, while conversely, phosphorylation of IRS at serine residues causes dissociation from the IR receptor and promotes its degradation by protesomes, therefore inhibiting downstream insulin signalling(Boura-Halfon and Zick, 2009; Zick, 2001). This suggests that maintaining the stability of IRS acts as a critical link in the insulin signalling pathway and can determine the extent of insulin's actions.

Activation of its downstream pathways can be simplified into 2 main branches: the Raf-1/MEK-MAP-K (mitogen associated protein kinase)/ERK (extracellular signal regulated kinase) and (PI3K)/protein kinase B(AKT) pathways which can modulate multiple downstream effectors including glycogen synthase kinase-3B (GSK-3B), mammalian target of rapamycin (mTOR), caspase-9 and transcription factor FoxO (forkhead box O1). These various effectors regulate a variety of important functions that are typically disrupted in PD including apoptosis, autophagy, inflammation, nerve cell metabolism, protein synthesis and synaptic plasticity (Hirsch et al., 2013; Schapira, 2008). Therefore it is perhaps unsurprising that insulin signalling has been shown to ultimately enhance neuronal survival. Additionally, via glucosensing neurons at the level of the hypothalamus, insulin regulates body weight, energy homeostasis and peripheral metabolism of lipids and glucose(Marino et al., 2011), and therefore alteration of brain insulin signalling can potentially lead to brain (and whole body) changes in energy metabolism.

2.3 Evidence for neuronal insulin resistance in Parkinson's disease

Age is the biggest risk factor for PD, and normal ageing is associated with a decrease in peripheral insulin receptor sensitivity. Studies indicate mRNA levels of insulin receptors in the brain decline in age, particularly in the hypothalamus, cortex and hippocampus, and this leads to chronic secondary hyperinsulinaemia (Kushner, 2013; W.-Q. Zhao et al., 2004). However, this physiological age-related decline in insulin signalling seems to be enhanced in PD. Studies

show marked loss of insulin receptor mRNA in the substantia nigra pars compacta (SNpc) of patients with PD and increased insulin resistance compared with age matched controls(Duarte et al., 2012; Morris et al., 2014; Takahashi et al., 1996). In addition, increased levels of IRS phosphorylation at serine residues (which deactivates insulin signalling) are also found in the basal ganglia and substantia nigra (Moroo et al., 1994). Furthermore, it has been shown that these changes may precede the death of dopaminergic neurons (Moroo et al., 1994).

Similar reductions in insulin and IGF-1 signalling has been observed in both PD and DLB brains, with significantly greater loss of IGF-1 in the frontal cortex in post mortem examinations of patients with DLB compared to PD associated with increased markers of oxidative stress and alpha-synuclein accumulation (Tong et al., 2009). Interestingly, the authors noted that manganese, an environmental toxin previously associated with the development of parkinsonism, caused similar evidence of insulin resistance and PD and DLB-associated abnormalities in primary cerebellar neuronal cultures, suggesting a possible common underlying mechanism of toxicity.

Recent studies have also shown that newly diagnosed patients with PD have raised levels of IGF-1 in the serum and CSF compared to controls which correlate with motor severity (Godau et al., 2011; Mashayekhi et al., 2010). It is not yet clear how these findings relate to the pathogenesis of PD, or how/if peripheral secretion of IGF-1 interacts with central IGF-1 to cause dysfunction. One theory is that raised levels of IGF-1 seen in the CSF are produced by prolonged microglial activation (Torres-Aleman, 2010) as a response to the degenerative changes in PD, but this remains to be confirmed.

Reduced levels of insulin and IR's are by themselves not sufficient evidence that insulin resistance is a pathological feature of PD, nor is the relationship specific to PD. Similar links between insulin resistance and AD exist, and true insulin resistance (reduced tissue responsiveness to the action of insulin) has recently been demonstrated in ex vivo studies and in patients with mild cognitive impairment (MCI). Insulin applied to hippocampal tissue from MCI patients induced less activation of the IR→IRS-1→PI3K/AKT pathway in hippocampal tissue compared to healthy tissue. Interestingly, significantly less activation of the same pathway

occurred when comparing established AD patients to healthy controls, despite increasing the dose of insulin tenfold (Talbot and Wang, 2014; Talbot et al., 2012).These findings were associated with elevated levels of phosphorylated IRS-1 at serine residues 636 and 616. As 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. This is consistent with other studies which have also demonstrated elevated levels of IRS-1 pSer312 and pSer616 in association with neuronal insulin resistance in AD (Moloney et al., 2010), leading some to propose that the detection of elevated levels of IRS-1 pS could act as a putative biomarker for neuronal insulin resistance in AD.

Perhaps indicative of similar mechanisms of insulin resistance in PD, recent studies have demonstrated elevated levels of IRS-1 pSer312 in neurons in the putamen of PD patients compared to controls (Bassil et al., 2015) while increased levels of pSer616 has also been found in hippocampal tissue of PD and PDD patients compared with controls. Similarly, increased levels of phosphorylated IRS at serine residues are seen in the dopamine-depleted striatum, but not skeletal muscle, in the 6-OHDA toxin model of PD and transgenic mice overexpressing alpha-synuclein (Gao et al., 2015; J K Morris et al., 2011; J.K. Morris et al., 2011; Morris et al., 2008).

However, it is remains to be seen whether this brain insulin resistance is due to impaired transit of insulin through the blood brain barrier, or if the neurons themselves become directly insensitive to the actions of insulin or a combination of both. Peripherally produced insulin does cross the blood brain barrier and can induce effects in the brain, especially the hypothalamus, but studies showing that hypo- and hyper-insulinaemia have little effect on total brain insulin suggest that outside the hypothalamus, brain insulin resistance may be due to reduced responsiveness to endogenous, rather than pancreatic produced insulin (Talbot and Wang, 2014).

2.4 Consequences of defective insulin signalling in PD - evidence from animal models

The relevance of defective insulin signalling to PD is that it seems be associated with worse clinico-pathological outcomes. Insulin resistance in patients with PD is associated with a more severe phenotype, accelerated disease progression and increased risk of cognitive decline, while in experimental models, it is associated with enhanced dopaminergic degeneration and both motor and cognitive deficits. Despite apaucity of experimental models that combine both PD and T2DM pathology in a single model, rodent models of insulin resistance and T2DM have been developed which display not only common metabolic abnormalities including peripheral insulin resistance but also neuronal insulin resistance – allowing them to be utilised to explore the interactions between insulin resistance and PD (Reagan, 2012).

Studies show that mice fed a high-fat diet to induce impaired insulin signalling and resistance have an increased vulnerability to toxins 6-OHDA and MPTP, leading to significantly increased nigrostriatal neurodegeneration and reduced dopaminergic signalling, resulting in enhanced motor deficits compared to matched controls (Choi et al., 2005; J.K. Morris et al., 2011; Morris et al., 2010). Similarly, PD pathology can be exacerbated by insulin resistance. Diabetic mice models treated with MPTP showed evidence of accelerated glial cell activation and loss of DA neurons accompanied by raised production of pro-inflammatory cytokines and alpha-synuclein in both the pancreas and midbrain (L. Wang et al., 2014).

In addition, insulin resistance may also be linked with the development of non motor symptoms. Studies show that brain/neuron-specific insulin receptor knockout (NIRKO) mice develop age-related anxiety and depressive behaviours, thought to be due to altered mitochondrial and monoamine oxidase A and B activity leading to increased dopamine turnover, as a direct result of loss of insulin signalling (Kleinridders et al., 2015). Interestingly, restoration of insulin sensitivity may restore these neuropsychiatric symptoms. Normalising a high fat diet in rodents and using insulin sensitizing drugs has been shown to halt depressive behaviours (Sharma et al., 2012; Yamada et al., 2011).

Recently a novel transgenic mouse model overexpressing a cytosolic protein (PED/PEA-15) was developed in an attempt to generate a model more representative of neurological deficits linked to T2DM pathology (Perruolo et al., 2016) . These mice developed insulin resistance accompanied by a loss of dopaminergic neurons in the striatum resulting in hypokinetic movements resembling parkinsonism.

3. Insulin signalling and neurodegeneration in Parkinson's disease – the significance of AKT

Whether insulin resistance occurs as a cause or consequence of neurodegeneration (or both) is a fundamental question. AKT is an important downstream target of the insulin signalling pathway, and acts as a major regulator of physiological responses to normal ageing. Able to phosphorylate over 50 downstream protein substrates, AKT acts as a master regulator of cellular function(Greene et al., 2011), and despite the complexity of its multiple targets, broadly speaking, acts to enhance cellular survival.

Substantial evidence implicates that loss of control of AKT signalling is involved in a number of age-related diseases including T2DM and AD(Griffin et al., 2005). Growing evidence also suggests that altered AKT signalling may also be a key component of PD pathogenesis, providing a possible link between insulin resistance and neurodegeneration in PD(Greene et al., 2011). Post mortem studies of PD patients showed a reduction in phosphorylated AKT and total AKT in PD patients compared with controls(Malagelada et al., 2008; Timmons et al., 2009); and single polymorphisms in akt, which encode AKT, can increase an individual's risk for developing PD (and also T2DM)(Xiromerisiou et al., 2008). In addition, PINK1 mutations (a cause of autosomal recessive parkinsonism) are associated with diminished AKT activity. Results from experimental models indicate that inhibition of AKT signalling leads to dopaminergic cell death(Canal et al., 2014; Xu et al., 2014), and dysregulation of AKT signalling may affect expression of alpha-synuclein in PD (Kim et al., 2011).

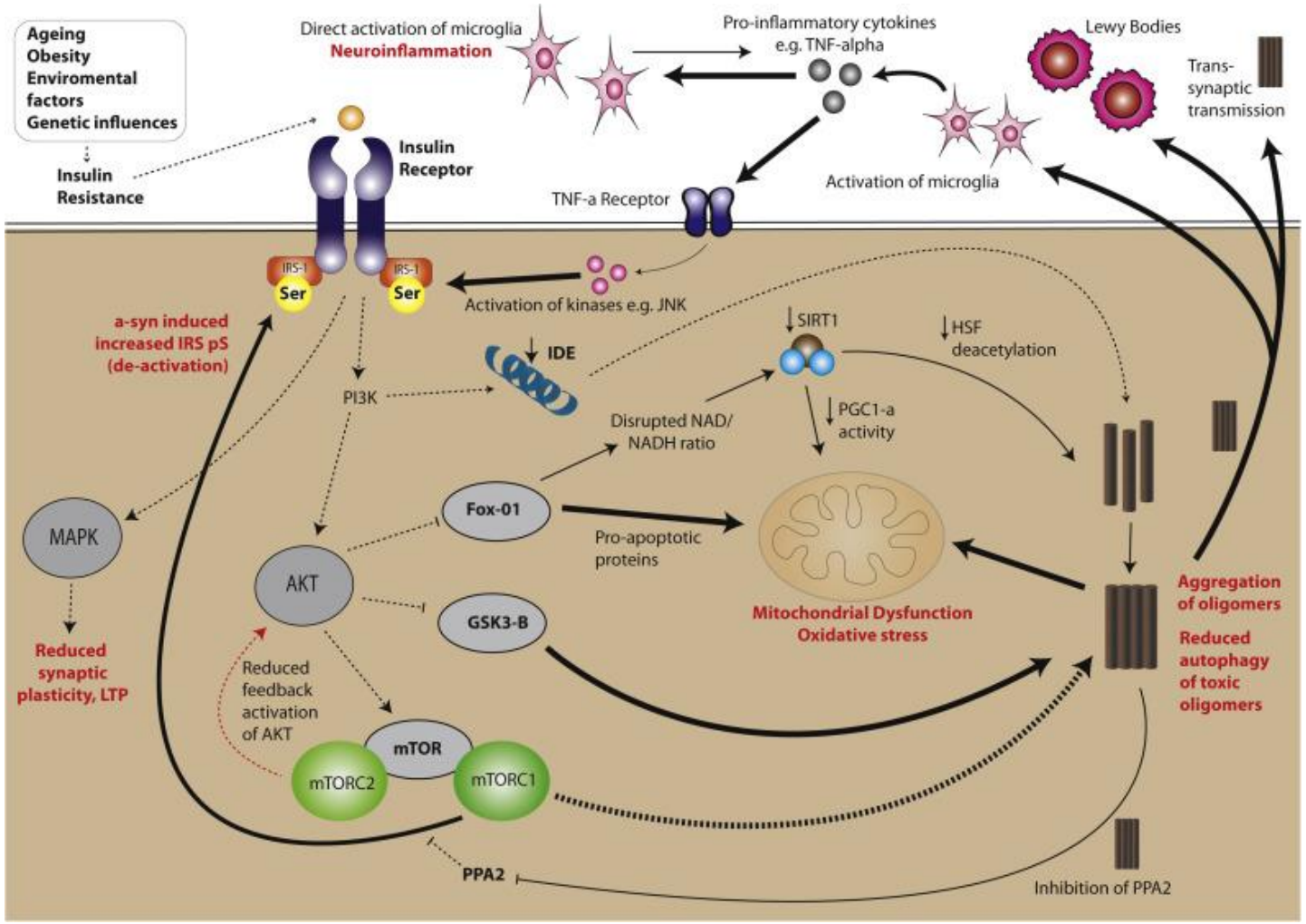
However, cell death in PD may not be as simple as loss of insulin receptor-stimulated phosphorylation of AKT as a consequence of insulin resistance. As with any biological system, negative feedback control of AKT is essential to maintain optimal tissue function. For example,

although AKT usually inactivates FoxO, physiological FoxO activity is a critical counter-balance to allow necessary transcription of stress response genes and repair systems(Kloet and Burgering, 2011; O' Neill, 2013). Further highlighting the importance of maintaining this balance are studies that demonstrate that reducing activation of PI3K/AKT can actually result in increased life spans(O' Neill, 2013), while sustained over activation of the AKT pathway has been linked to cancer and exacerbation of AD-related pathology(Griffin et al., 2005). This may partly explain seemingly paradoxical data from studies that show reduced insulin signalling actually promotes longevity in yeast, drosophila, mice and worms (Blüher et al., 2003; Pawlikowska et al., 2009; Taguchi et al., 2007; van Heemst et al., 2005) and delayed the effects of ageing(Selman et al., 2008) in rodents.

4. Influence of insulin signalling on PD pathogenesis

There are numerous steps in the insulin signalling pathway that can influence a variety of processes that can contribute to the development of PD (see Figure 1).

Figure 1 - In models of insulin resistance, accumulation of alpha-synuclein may ultimately exacerbate activation of the mTORC1 pathway and induce microglia activation, raising levels of TNF-alpha, leading to activation of stress kinases such as JNK, both of which lead to IRS phosphorylation at serine residues, exacerbating insulin resistance. Loss of the insulin signalling pathway reduces activation of the AKT pathway, promoting mitochondrial dysfunction, inflammation, oxidative stress and accumulation of alpha-synuclein (by reduction in autophagy and reduced activation of SIRT1).



4.1 Protein aggregation / autophagy

Dysfunction of lysosomal systems, disruption of normal processes through which cells degrade abnormal proteins/cellular constituents (autophagy) and the aggregation of alpha-synuclein into toxic fibrils, are thought to be critical steps in the process leading to degeneration of dopaminergic neurons in PD. Insulin signalling has been shown to influence lysosomal systems accompanied by increased expression of PD pathology (Matsuzaki et al., 2010; Willette et al., 2015).

Studies have shown that insulin signalling can modulate degradation of alpha-synuclein through activation of insulin degrading enzyme (IDE), a zinc-metalloendopeptidase that can degrade insulin and other small peptides that can form B-pleated sheets. Via activation of PI3K following IR activation, IDE can inhibit alpha-synuclein fibril formation by binding to alpha-synuclein oligomers, blocking them from forming fibres(Sharma et al., 2015). Correspondingly, induction of insulin signalling with IGF-1 or reversal of insulin resistance suppresses alpha-synuclein aggregation and toxicity(Kao, 2009).

Activation of the AKT pathway following insulin signalling also causes phosphorylation of GSK-3B at serine 9, causing its inactivation. GSK-3B is a multi-function kinase that enhances pathways that promote apoptosis, inflammation, mitochondrial dysfunction and alpha-synuclein expression (and Lewy body formation)(Golpich et al., 2015). Inhibition of GSK-3B promotes autophagy and has been shown to halt expression and aggregation of alpha-synuclein and its subsequent neurotoxic effects in vitro and in vivo(Duka et al., 2009; Yuan et al., 2015), while increased expression of GSK-3B has been found in PD patients and experimental models of PD associated with increased accumulation of alpha-synuclein(Hernandez-Baltazar et al., 2013; Wills et al., 2010). In a damaging feed forward loop, increased levels of alpha-synuclein can also inhibit IRS-1, causing increased activation GSK-3B activity, leading to further deleterious effects(Duka et al., 2009).

Dysfunction of autophagy is also implicated in neurodegeneration in PD. A key downstream target of the IR/PI3K/AKT pathway is the kinase mTOR, which when activated by AKT, inhibits excessive autophagy, promoting cell growth and survival. Conversely dysregulation of this

pathway has been reported in patients and experimental models of PD with associated autophagy disruption and abnormal clearance of proteins (Heras-Sandoval et al., 2014). Of its 2 component complexes, mTORC1 acts as a key negative regulator of autophagy (and also acts a primary negative feedback pathway, inactivating and degrading IRS-1), while mTORC2 is thought to activate AKT signalling. Therefore insulin, via activation of the PI3K/AKT/mTOR pathway, can promote cell growth and inhibit excessive autophagy leading to cell death, while inhibiting mTORC1 may enhance autophagy of toxic proteins and increase cellular survival through mTORC2 activity on AKT(Heras-Sandoval et al., 2014). Correspondingly, parallel studies show that compounds targeting inhibition of mTORC1 such as rapamycin can attenuate alpha-synuclein aggregation in models of PD; and also AB and tau misfolding in models of AD, and are being investigated as potential novel neuroprotective therapies (Caccamo et al., 2010; Stoica et al., 2011; Tain et al., 2009).

In addition, it is strongly speculated that alpha-synuclein spread from the brainstem to limbic and neocortical structures is the major contributor to emerging dementia in PDD and DLB. However, as described above, processes leading to the development of AD-related pathology (AB and plaques and hyperphosporylated tau containing neurofibrillary tangles) may also influence the initiation / acceleration of cognitive decline in PD/DLB or the development of superimposed AD in a subset of individuals with PD. Loss of central insulin sensitivity has also been shown to increase the formation of AD-related pathology in experimental models of AD and recent in vivo studies have shown insulin resistance can contribute to amyloid deposition in frontal and temporal areas in asymptomatic individuals (Willette et al., 2015).

Notably, insulin/IGF-1 can increase AB trafficking and clearance from the CNS by upregulating the expression of AB transporters in the CSF, via activation of the PI3K/MAPK pathway (Ashpole et al., 2015; Carro et al., 2002).

Similarly, insulin induced activation of IDE can also bind and degrade AB, halting their neurotoxic toxic effects in experimental models of AD (Qiu and Folstein, 2006; Sudoh et al., 2002; Vekrellis et al., 2000). IDE activity declines with increasing age, and reduced activity is found in patients and experimental models of AD(L. Zhao et al., 2004). Insulin resistance, either through

decreased activation of IDE, or competitive inhibition of IDE by insulin induced by prolonged hyperinsulinaemia, results in impaired autophagy and subsequent decreased turnover and/or neutralization of amyloidogenic proteins in β-cells (Steneberg et al., 2013), impaired degradation of Aβ and promotion of AD pathology (Ho et al., 2004; Leal et al., 2009). Importantly for possible therapeutic considerations, restoration of insulin sensitivity has been shown to reduces concentrations of AB in vivo through elevation of IDE (Gao et al., 2014).

As well as regulating levels of alpha-synuclein and Aβ, insulin can also mediate phosphorylated tau formation. Recent results from the Alzheimer's disease Neuroimaging initiative found that patients with concurrent T2DM had elevated levels of phosphorylated and total tau(Moran et al., 2015). This is particularly relevant in view of recent post mortem and genetic studies which implicate hyperphosphorylation of tau in the pathogenesis of PD and PDD (Wills et al., 2010). MAPT, the gene that encodes tau, has an H1/H1 subhaplotype which has been identified as an independent risk factor for the development of PD and PDD, and is associated with increased tau expression in humans and poor memory performance in PD. Via inhibition of GSK-3B, activation of the insulin pathway inhibits phosphorylation of tau and enhances binding of tau to microtubules, limiting its toxicity(Tokutake et al., 2012). Correspondingly, animal models of insulin resistance and NIRKO mice demonstrate increased phosphorylated tau and neurofibrillary tangles associated with reduced AKT and GSK3B phosphorylation (Cheng et al., 2005; Freude et al., 2009). Importantly, given the therapeutic implications, these effects could be reduced with restoration of insulin signalling using exogenous insulin (Jolivalt et al., 2008).

4.2 Mitochondrial function

Nigro-striatal neurons have some of the highest energy demands of any cell and are therefore vulnerable to events that interfere with mitochondrial function. In parallel, significant evidence suggests that processes that affect mitochondrial function such as defective mitophagy, increased accumulation of mDNA mutations, defects of complex I of the respiratory chain, dysregulated mitochondrial calcium homeostasis and increased oxidative stress are all involved in the pathogenesis of PD(Schapira, 2008). Through activation of the IR→PI3K→AKT pathway,

insulin can modulate mitochondrial electron transport chain activity by suppressing FoxO1/HMOX1 activity and maintaining the NAD(+)/NADH ratio, which mediates the SIRT1/PGC1α pathway, and acts as a master regulator of mitochondrial biogenesis(Cheng et al., 2010). Correspondingly, experimental models of insulin resistance demonstrate altered levels of mitochondrial proteins in the substantia nigra (Khang et al., 2015), and demonstrate reduced levels of mitochondrial complex I and dysregulated calcium homeostasis(Duarte et al., 2013; Moreira et al., 2006). These processes negatively affect mitochondrial biogenesis, inducing membrane depolarisation and leading to the generation of excessive ROS, oxidative stress and enhanced cell death (Huang et al., 2003; Kleinridders et al., 2015).

Reduced expression of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1a) is one of the earliest features of insulin resistance(Mootha et al., 2003), and growing evidence suggests dysregulated PGC-1a activity may play a critical role in the pathogenesis of PD. GWAS studies have indicated down regulation of PGC-1a responsive genes occurs in patients with early stage PD (Zheng et al., 2010a); PGC-1a polymorphisms are associated with increased risk of early onset PD(Clark et al., 2011); and in vitro studies indicate loss of PGC-1a is associated with increased accumulation of alpha-synuclein(Ebrahim et al., 2010). Conversely, overexpression or activation of PGC-1a protects dopaminergic neurons from MPTP-induced degeneration in vivo, enhances mitochondrial biogenesis and prevents alpha-synuclein induced DA neuronal loss(Zheng et al., 2010b).

Recent studies have also shown that PARIS, a zinc finger protein highly expressed in the substantia nigra of patients with parkin-related parkinsonism and also sporadic PD, represses expression of PGC-1a and its target gene NRF-1, leading to neurodegeneration in models of PD(Corona and Duchen, 2015a). Interestingly, this site of interaction between PARIS and PGC-1a is a sequence that is involved in the regulation of insulin responsiveness and energy metabolism, leading some to speculate that loss of expression of PGC1 controlled genes may be a key link between abnormal mitochondrial function, glucose utilization and PD (Aviles-Olmos et al., 2013b). Recently, it has also been shown that chronic insulin resistance in mice disrupts the Parkin–PARIS–PGC-1α pathway, causing reduced levels of parkin, accumulation of PARIS, and downregulation of PGC-1a, leading to degeneration of dopaminergic neurons and increasing

their vulnerability to MPP+, providing a putative mechanism linking insulin resistance, mitochondrial dysfunction and neuronal degeneration(Khang et al., 2015).

4.3 Cerebral glucose metabolism

There may also be a relevant relationship between neurodegeneration, insulin signalling and glucose utilisation in the brain. Using FDG-(2-[18F]fluoro-2-deoxy-D-glucose)-PET (positron-emission tomography) imaging, studies have shown patients with PD exhibit widespread cortical hypo-metabolism compared to controls, that is evident even in the early stage(Borghammer et al., 2010).

Similarly, cognitive decline in PD may also be linked to abnormal cerebral glucose metabolism. Significantly pronounced glucose hypo-metabolism in the frontal and parietal cortices is seen in patients with PD-MCI and PDD compared to age matched controls(Hosokai et al., 2009; Huang et al., 2008; Liepelt et al., 2009; Yong et al., 2007) and may predict cognitive decline (Dunn et al., 2014; Peppard et al., 1992).

In parallel, studies have found that in healthy individuals peripheral insulin resistance is associated with cerebral glucose hypo-metabolism in the parietotemporal, frontal, and cingulate cortices(Baker et al., 2011) and may predict worse memory performance (Willette et al., 2015b). Perhaps indicative of the heterogeneous nature of pathophysiology underlying cognitive impairment in PD, these patterns of cerebral regional hypo-metabolism are also seen in early stage AD, leading some to suggest insulin resistance may act as putative biomarker identifying patients at risk of developing cognitive decline and AD (Baker et al., 2011; Willette et al., 2015a, 2015b)

Reduced cerebral glucose metabolism causes an increase in intracellular ATP/ADP, inactivating potassium channels, which modulate dopamine release from dopaminergic neurons (Levin, 2000), and increase the risk of cognitive decline(Willette et al., 2015b, 2013). Although this hypometabolism may not directly be related to neuronal insulin resistance as insulin does not directly affect neuronal glucose uptake, this reduced cerebral glucose metabolism may occur as

a secondary consequence of reduced postsynaptic neurotransmission (resulting from reduced insulin signalling), as glutamate and other agents stimulate glucose uptake in the brain (Talbot and Wang, 2014).

4.4 Oxidative stress and neuroinflammation

Abnormal insulin signalling may also be linked with extracellular events of relevance to neurodegeneration. Inflammation is increasingly recognised as a key contributor to the pathogenesis of PD. Epidemiological studies suggest NSAID use confers a decreased risk of developing PD(Rees et al., 2011); PET imaging of patients with PD shows increased microglial activation (Bartels et al., 2010); and increased pro-inflammatory mediators are seen in the substantia nigra at post-mortem examination(Imamura et al., 2003). Moreover, genome-wide association studies have reported an association between certain HLA alleles and the risk of PD (Hamza et al., 2010).

Microglia play a critical role in neuroinflammation in PD (see (Joers et al., 2016) for reivew). While microglial activation may initially be protective in the early stages, prolonged activation is severely damaging as disease progresses (Sekiyama et al., 2012), and can be further propagated by alpha-synuclein, cytokines, and neuronal death, and thus is a major factor in driving dopaminergic degeneration in PD. Various branches of in the insulin signalling pathway have been shown to influence microglial activation. Studies have shown that PI3K/MAPK, via NADPH oxidase activation can halt the microglia response and subsequent DA degeneration in PD (Jha et al., 2015; Wang et al., 2011).

An important downstream effector of the IR/PI3K/AKT pathway is nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). As a transcription factor that mediates the pro-inflammatory response of microglia and as a master regulator for inflammatory gene expression, NF-κB regulation has been implicated in the pathogenesis of neuro-inflammation in PD. Increased NF-κB activity has been found in TH+ dopaminergic neurons, astrocytes and microglia in the SNpc of patients with PD and animal models(Hunot et al., 1997), and accordingly inhibition of NF-κB is neuroprotective in models of PD (A. Ghosh et al., 2007; Zhang et al., 2010). Although extensive crosstalk exists between NF-κB and other factors (as various pro-

inflammatory mediators can directly activate NF-κB(Oeckinghaus et al., 2011)), a recent study showed that up-regulation of the AKT pathway up-regulated IκBα, a specific endogenous inhibitor of NF-κB, resulting in reduced neuroinflammation(Khasnavis et al., 2012), suggesting a possible mechanism linking insulin signalling and neuroinflammation.

Chronic glucose dysmetabolism as a result of insulin resistance may also lead to the formation of advanced glycation endproducts (AGEs). Interaction with its receptor RAGE (the receptor for advanced glycation end products) triggers multiple intracellular signalling pathways including activation of the pro-inflammatory-associated transcription factor NF-kB, leading to increased oxidative stress, inflammation and neuronal cell death. AGE and RAGE levels are increased in the frontal cortex of PD patients, and also promote the aggregation of alpha-synuclein and the formation of Lewy bodies(Castellani et al., 1996; Dalfó et al., 2005; Jinlong Li et al., 2012).

Taken together, it is clear that inflammation and insulin resistance may exert a reciprocal relationship. On one hand, insulin resistance may induce production of pro-inflammatory cytokines leading to cell death, and also further reduce insulin sensitivity by feedback inhibition of the insulin receptor. Simultaneously, through a feed-forward mechanism, inflammation induces mitochondrial dysfunction, driving overproduction of reactive oxygen species production to further the inflammatory state (Dineley et al., 2014), thus enhancing neurodegeneration.

4.5 Synaptic transmission and memory

The clinical phenotype of PD evolves not only due to neurodegeneration but also due to abnormal patterns of firing of interconnected neuronal pathways, leading to dysfunctional synaptic plasticity, and has been implicated in the initial onset of PD (Picconi et al., 2012; Schroll et al., 2014). Insulin, via modulation of mTORC1 activity, has been shown to regulate synaptic plasticity by controlling synapse density and regulation of PSD95, a scaffold protein needed for the formation of the synaptic junction and dopamine-mediated synaptic and behavioural plasticity (Chiu et al., 2008; Lee et al., 2005; Yao et al., 2004). Abnormal synaptic plasticity also has relevance in the development of the motor complications of PD such as levodopa-induced dyskinesia (Calabresi et al., 2013; Picconi et al., 2012), and also may partially contribute to the complex evolution of cognitive impairment.

Dementia is common in the advanced stages of PD, affecting up to 80% of patients(Hely et al., 2008), and often heralds impending residential care and mortality. However mild cognitive impairment can occur early in the course of PD and a quarter of patients already have evidence of cognitive deficits already at diagnosis (Foltynie et al., 2004; Williams-Gray et al., 2013, 2009). The hippocampus is known for its role as an integrator of memory formation, and studies suggest alterations in hippocampal structure and function areimplicated in cognitive decline in PD (Bouchard et al., 2008; Costa et al., 2012); correlate positively with memory defects and behavioural abnormalities (Bouchard et al., 2008; Ibarretxe-Bilbao et al., 2008); and may predict progression to PDD(Pan et al., 2013). Furthermore, the high energy demands of hippocampal neurons means they are especially vulnerable to alterations in insulin sensitivity(Fehm et al., 2006), supported by studies showing that insulin resistance and T2DM are associated with increased risk of cognitive decline and AD.

The role of insulin in modulating cognition is suggested in part by the high density of IR's evident in the hippocampus, cortex and amygdala, which are shown to be upregulated in response to spatial memory training(W.-Q. Zhao et al., 2004). Furthermore, acute administration of insulin improves performance on memory tasks in rats, and enhances verbal memory, attention and cognition in humans (Blázquez et al., 2014; Park et al., 2000) thought to be due to activation of hippocampal insulin receptors. However, conflicting evidence from studies using NIRKO mice demonstrate no alteration in memory performance, suggesting other mechanisms may also contribute (Schubert et al., 2004). Nevertheless, accumulating evidence indicates insulin plays a significant role in cognition and although the underlying molecular mechanisms remain unclear, studies indicate hippocampal insulin resistance is a risk factor for cognitive impairment and dementia in AD (Biessels and Reagan, 2015).

Insulin's effects on cognition seem to be dependent on activation of the PI3K/MAPK pathway(McNay et al., 2010) and may be mediated by its ability to modulate synaptic plasticity, density, and neurotransmission as well as perhaps neurogenesis (Steculorum et al., 2014). Rodents fed a high-fat diet to induce neuronal insulin resistance show decreased expression of PSD-95, a scaffolding protein enriched in post-synaptic densities, and synaptopodin, an actin-

associated protein enriched in spine apparatuses, resulting in impaired spatial working memory (Arnold et al., 2014).

Activation of the PI3K/MAPK/ERK pathway also mediates glutamate and g-aminobutyric acid receptors, enhances protein synthesis and maintains dendritic spine stabilisation, shown to be essential for hippocampal long term potentiation (LTP) and memory consolidation(Goldin M, 2003; Zhao and Townsend, 2009).

4.6 Neurogenesis

Post mortem studies suggest that the age-related decline in adult neurogenesis may be accelerated in patients with PD (Höglinger et al., 2004; O'Keeffe et al., 2009), possibly due to dopaminergic depletion having a negative effect on cellular proliferation(Lamm et al., 2014; Regensburger et al., 2014), and while the relationships are not entirely understood, altered neurogenesis in the hippocampus in PD(Höglinger et al., 2004) may be linked with impairments not only in memory processing, but also in olfaction, and depression(Carlesimo et al., 2012; Regensburger et al., 2014). Insulin signalling, via activation of the PI3K/AKT pathway has positive effects on enhancing neurogenesis while conversely in rodent models of diabetes and insulin resistance, is associated with significantly altered hippocampal atrophy and neurogenesis(Ramos-Rodriguez et al., 2014).

In summary, insulin signalling can mediate a number of cellular processes implicated in PD pathogenesis and evidence from experimental models suggests insulin resistance can drive and/or exacerbate PD pathology.

5. Causes of insulin resistance

Although several studies have demonstrated resistance in association with neurodegenerative disorders, we must return to the question whether the observed insulin resistance is a cause or consequence of neurodegeneration. While the aetiology of decreased brain insulin signalling that

is thought to occur in PD are still yet to be elucidated, recent GWAS have identified strong common links between PD, diabetes and inflammation(Moran and Graeber, 2008).

Although encompassing two separate pathologies, parallels may be able to drawn from studies investigating insulin resistance in AD, which suggest dysfunctional IRS-1 as the most likely proximal cause of insulin resistance(Talbot and Wang, 2014). This is supported by multiple studies demonstrating elevated levels of IRS-1 pS found in the cerebral cortex and hippocampus of AD patients.

Given that recent studies have demonstrated similar elevated levels of IRS-1 pS in the SNpc in patients and animal models of PD, and in view of its established role in causing peripheral insulin resistance and its critical function in the insulin signalling pathway, it is reasonable to infer that maintaining the stability of IRS-1 may also play a key role in the aetiology of insulin resistance in PD.

Studies suggest that in peripheral insulin resistance and neuronal insulin resistance in AD, both prolonged metabolic stress and AB induce the production of pro-inflammatory cytokines such as TNF-alpha, IL-1, IL-6, which in turn phosphorylate and activate IRS-1 serine kinases IKK, JNK and Erk2. This ultimately leads to phosphorylation of IRS-1 at serine residues – thereby inactivating and inhibiting downstream insulin signalling and leading to the development of peripheral and neuronal insulin resistance(De Felice et al., 2014; Ferreira et al., 2014; Hirosumi et al., 2002; Santos, Fernando R, Diamond-Stanic, 2012).

5.1 The role of alpha-synuclein in insulin resistance in Parkinson's disease

Similar mechanisms may underlie the development of insulin resistance in PD (Figure 1). Alpha-synuclein has been shown to increase phosphorylation of IRS at serine residues (inactivating IRS) ultimately leading to supressed insulin signalling(Gao et al., 2015), suggesting alpha-synuclein may negatively regulate insulin signalling. The molecular mechanisms underlying this process are not yet known, though one study suggests alpha-synuclein causes sustained mTORC1 activation, enhancing the insulin signalling negative feedback loop and increasing

degradation of IRS-1, and inhibiting protein phosphatase (PP)2A activity, usually involved in inhibiting this mTORC1/S6K1 feedback IRS-1 degrading pathway(Gao et al., 2015). Alternatively, this vicious cycle may be exacerbated as a result of alpha-synuclein-induced microglial production of pro-inflammatory cytokines. Studies indicate alpha-synuclein can directly activate microglia or induce the evolution of microglia to the cytotoxic M1 phenotype(Béraud et al., 2013; Blandini, 2013; Gallegos et al., 2015), leading to the release of pro-inflammatory cytokines. Post mortem studies have also shown evidence of overproduction of pro-inflammatory cytokines including TNF-alpha in the CSF and SN of patients with PD (Dobbs et al., 1999; Reale et al., 2009a, 2009b).

The interaction between low grade inflammation and insulin signalling is thought to be important in the evolution of both peripheral and neuronal insulin resistance, and in parallel with this, peripherally derived sources of pro-inflammatory molecules have also been shown to influence the pathogenesis of PD (Perry et al., 2007). Normal ageing appears to be associated with chronic low grade systemic and neuro-inflammation (Kanaan et al., 2010), and interestingly, this seems to be enhanced in PD. A recent meta-analysis of studies assessing peripheral cytokines in patients with PD indicated consistently higher peripheral concentrations of IL-6, TNF-a, IL-1β, IL-2, IL-10 and C-reactive protein in patients in PD compared with aged matched controls (Qin et al., 2016).In addition a recent study of newly diagnosed patients with PD showed that patients with a higher proportion of pro-inflammatory markers (IFN-y, TNF-a, IL-6, IL-10) were associated with lower cognitive assessment scores (MMSE) and more rapid motor decline, whereas subjects with higher anti-inflammatory cytokines (IL-4, IL-13) were associated with better cognitive function and stable motor function (Williams-Gray et al., 2016). Similar elevated levels of pro-inflammatory cytokines are also found in the CNS(Dobbs et al., 1999; Kanaan et al., 2010; Mogi et al., 1994; Reale et al., 2009b). In conjunction, obesity (or rather increased adiposity) and metabolic syndrome (Chen et al., 2014), both risk factors for PD, are also associated with an elevated production of pro-inflammatory cytokines.

During this state of chronic low grade inflammation due to ageing, obesity and metabolic stress, pro-inflammatory cytokines can cross the blood brain barrier and directly induce cell death and/or activate IRS serine kinases such as JNK (in a similar manner to activated microglia) to induce

neuronal insulin resistance (Gonzales et al., 2012; Hsuchou et al., 2012). In concordance with this, recent studies have demonstrated elevated levels of phosphorylated JNK in the serum of patients with PD compared to controls (S. Wang et al., 2014). This may somewhat explain why animal models of peripheral insulin resistance and obesity/high fat diet models show increased CNS macrophage infiltration and activation within the hypothalamus and exaggerated responses to peripherally administered toxins, indicating a priming of microglial cells (Cunningham and Hennessy, 2015; Spielman et al., 2014).

Innate immune responses in PD can therefore become activated as a result of ageing, metabolic stress and genetic influences which can either directly lead to neuronal insulin resistance or influence cell death directly, activating further inflammatory pathways, enhancing neurodegeneration, contributing to PD pathogenesis and perpetuating the disease process (Ferreira et al., 2014).

Taken together, alpha-synuclein may drive defective insulin signalling in PD due to inappropriate activation of the P13K/AKT/mTORC1 pathway and also due to alpha-synuclein induced activation of JNK. Together with a reduction in normal insulin/IGF-1 responses (insulin resistance), this leads to loss of AKT homeostasis and the protective effects of FoxO activation and GSK-3B inactivation, resulting in further exacerbation of alpha-synuclein (and in models of AD, AB and tau) pathology and dopaminergic cell loss. Furthermore, studies suggest alpha-synuclein induced insulin resistance may induce further alpha synuclein aggregation and thus perpetuate a vicious cycle.

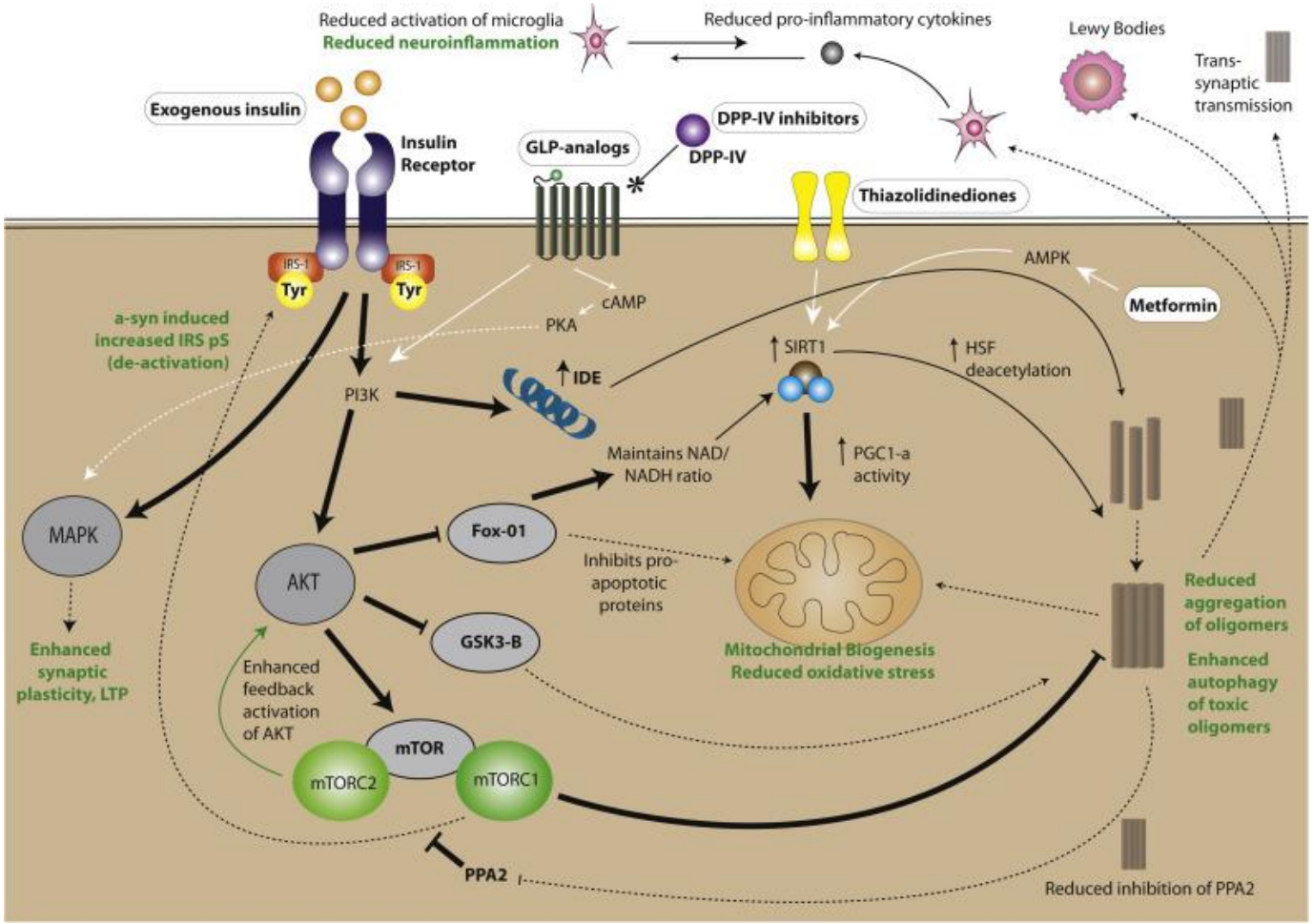
6. Targeting insulin resistance as a potential therapeutic strategy

Although it remains to be conclusively shown whether dysregulated insulin signalling is a primary contribution to PD or a secondary consequence of the neurodegenerative process, defective insulin signalling is increasingly recognised in its association with PD. Given the growing links between PD and T2DM it is perhaps not surprising that drugs used the treatment of T2DM are

amongst the most promising treatments currently being prioritised for repositioning as possible novel treatments for PD (Brundin et al., 2013) in an attempt to restore this signalling pathway.

Supporting this are recent epidemiological data which indicates that anti-glycaemic drugs seem to reduce the risk of developing PD, despite varying putative mechanisms of action (Brauer et al., 2015; Svenningsson et al., 2016; Wahlqvist et al., 2012), suggesting that as well at their effects at restoring insulin sensitivity, there may be various “off-target” effects related to the insulin signalling pathway that may be of relevance to neurodegeneration in PD (see Figure 2).

Figure 2 - The influence of anti-glycaemic drugs on insulin resistance and PD pathogenesis.



Also the growing evidence supporting the role of AB and tau in the development of cognitive decline in PD has led some to speculate that potential disease modifying agents that target AD-related pathology may also be of benefit to a subset of patients with PDD. Therefore the effects anti-glycaemic drugs on typical AD-related pathology will also be discussed.

Although all the classes of drugs currently used in the treatment of diabetes may potentially indirectly offer beneficial effects in PD through effects on metabolism, oxidative stress and inflammation, neuronal insulin resistance is thought most closely linked to PD pathology and so drugs that can effectively cross the blood brain barrier and ideally affect the insulin signalling pathway would potentially be the most efficacious. We will review a variety of interventions/drugs used in diabetes to assess their potential in PD.

6.1 Lifestyle modifications

Studies show that the prevalence of peripheral insulin resistance rises in middle age, and as previously noted, may exacerbate brain insulin resistance. This is supported by studies showing a decline in IR and an increase in brain IRS-1 pS616 in ageing. As well as genetic influences, environmental factors play an important role in disease aetiology and progression in PD. In parallel with strategies in diabetes management which indicate that lifestyle changes may slow or halt the progression of peripheral insulin resistance to diabetes, encouraging lifestyles to reduce peripheral insulin resistance in this age group may ultimately reduce the risk of not only progressing to T2DM but also developing PD (although the difficulty in early identification of patients at high risk of developing PD still remains).

While evidence is scarce, interestingly, interventions that improve peripheral insulin resistance such as adhering to a Mediterranean diet, having a low/normal BMI and regular exercise and other dietary factors also seem to be associated with a reduced risk of developing PD(Ebert et al., 2008; Hsuchou et al., 2012; Sun et al., 2010), though it is unproven whether initiating these lifestyle changes after diagnosis would restore insulin sensitivity.

6.2 Insulin

One seemingly intuitive strategy to augment reduced brain insulin signalling is with the use of exogenous insulin/IGF-1. Results from experimental models of PD have supported this approach: studies demonstrate overexpression of IGF-1 protects dopaminergic neurons from 6-OHDA and MPTP-induced cell death and also by alpha-synuclein induced toxicity (Ayadi et al., 2016; Ebert et al., 2008; Krishnamurthi et al., 2004; Sun et al., 2010; Zhang et al., 2015). Neuroprotection was accompanied by elevation of phosphor-Akt (Ser473) and inhibition of GSK-3B (Ayadi et al., 2016) and improvements in both motor and behavioural functional deficits (Krishnamurthi et al., 2004).

Although no data yet exists from human trials utilising exogenous insulin in patients with PD, recent clinical trials in AD/MCI have shown the potential utility of using insulin to restore insulin signalling defects. To avoid the obvious risks of peripherally administering insulin to non-diabetic patients, trials of intranasal insulin (to limit systemic effects on blood glucose) was administered to patients with MCI and early AD (M A Reger et al., 2008; Mark A Reger et al., 2008). This led to improvements in verbal memory and cognition, AB 1–40/1–42 ratio in the CSF, and increased cortical activation as seen in FDG-PET scans (Freiherr et al., 2013; Shemesh et al., 2012; Zhang et al., 2015). It remains to be seen whether these improvements in AD pathology and cerebral glucose metabolism would be beneficial in halting cognitive decline in patients with PD.

While the improvements in cognition were sustained 2 months after cessation of insulin administration, long term use of intranasal insulin in neurodegenerative diseases may in theory be limited by a number of important factors. Studies show continuous insulin use may actually increase insulin desensitization (van der Heide et al., 2006) and potentiate NMDA receptors leading to increased excitotoxicty and cell damage. A further concern is that insulin is unlikely to overcome the levels of insulin resistance in advanced PD. However, its maximal therapeutic implications may be in the early stages by preventing oligomer induced synapse and IR toxicity. A multi-centre, phase 2/3 study investigating the use of intranasal insulin in 240 patients with MCI or AD has completed recruitment and currently ongoing (Clinical trials.gov NCT01767909).

6.3 Thiazolidinediones

The thiazolidinediones are a class of drugs that increase insulin sensitivity by acting as selective ligands of the peroxisome proliferator-activated receptor gamma (PPARγ) receptor. PPARγ receptors are expressed in insulin sensitive tissues such as liver and pancreas, but are also expressed in nigral and putaminal nuclei(Swanson and Emborg, 2014). Two drugs of this class, rosiglitazone and pioglitazone have been used as insulin sensitizing agents for the treatment of non-insulin dependent diabetes (Leonardini et al., 2009). Thiazolidinediones can reduce peripheral insulin resistance through interaction with hepatocyte nuclear factor (HNF4-a) and Fox01, which can mediate whole body insulin sensitivity by modulating expression of genes involved in lipid metabolism. By increasing adiponectin expression and reducing levels of circulating free fatty acids by enhancing adipogenesis, this drives free fatty acid uptake and storage in adipose tissue, thereby providing a "metabolically safe" place to store fat, limiting its influence on other systems(Soccio et al., 2014) including neuronal insulin resistance and neurodegeneration. Although the highest density of PPARy receptors are found in adipose tissue, a recent study also found that neuronal PPARy receptors also mediate hepatic insulin sensitivity in animals fed a high fat diet(Lu et al., 2011).

A recent retrospective cohort study involving over 160,000 diabetes patients from a healthcare database revealed that concurrent use of glitazones was associated with a 28% lower rate of presentation of PD compared to the use of other diabetic drugs (IRR 0.72)(Brauer et al., 2015). Pioglitazone and rosiglitazone have also demonstrated neuroprotective effects across a range of animal toxin models of PD, including the MPTP(Dehmer et al., 2004; Laloux et al., 2012; Quinn et al., 2008; Schintu N, Frau L, Ibba M, Caboni P, Garau A, Carboni E, 2009; Swanson et al., 2011), LPS (Hunter et al., 2008), 6-OHDA (Lee et al., 2012) and rotenone models(Corona et al., 2014) resulting in improvements in behavioural and motor responses.

As well as its role in regulation of glucose and lipid metabolism, activation of the PPARy receptor modulates expression of a number of genes that regulate inflammatory cascades, mitochondrial function and oxidative stress responses(Corona and Duchen, 2015b) which may explain their protective effects in these models of PD. For example, PPARy activation can inhibit expression of STAT3 and MMP3 which induce microglial activation, and also directly inhibit pro-inflammatory

cascades induced by microglia(Swanson et al., 2011)(Sadeghian et al., 2012; Shibata et al., 2010), limiting deleterious effects.

PPARy activation can also influence mitochondrial function through interaction with PGC-1a - a master regulator of mitochondrial biogenesis and respiration, and identified as a potential valuable target in PD and other neurodegenerative diseases. Studies show thiazolidinediones, via activation of PGC1-a, can enhance mitochondrial biogenesis in neurons by influencing a number of cellular processes. These include direct stabilisation of MitoNEET (an outer mitochondrial membrane protein which regulates oxidative phosphorylation)(S. Ghosh et al., 2007; Paddock ML, Wiley SE, Axelrod HL, Cohen AE, Roy M, Abresch EC, Capraro D, Murphy AN, Nechushtai R, Dixon JE, 2007); enhancing the expression of electron complex I and mitochondrial transcription factor (TFAM); reducing oxidative stress via upregulation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2), a key transcription factor that modulates antioxidant response elements and reduces free radical formation(Corona et al., 2014); and inhibiting apoptosis by inducing expression of antioxidant enzymes SOD1 and SOD2, and upregulating expression of Bcl-2 and Bax to the mitochondria to inhibit caspase3 induced cell death (Jung et al., 2006)(Thouennon et al., 2015).

Despite the promising pre-clinical data – results from human trials using thiazolidinediones in PD have been disappointing. A randomised controlled trial of pioglitazone was recently completed and involved 210 early stage PD patients on monoamine oxidase B (MAO-B) inhibitors only, assigned to placebo, 15mg pioglitazone or 45mg pioglitazone. The primary outcome – change in total UPDRS score – showed no difference between placebo and treatment arms after 44 weeks (NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators., 2015).

In parallel, encouraging pre-clinical effects on cognition and AD-related pathology have also been observed with glitazone use. A recent prospective cohort study of 145,928 patients indicated that long term use of pioglitazone in diabetics reduced the dementia risk by 47% (RR0.53, p= 0.029) compared to non-diabetics (Heneka MT, Fink A, 2015). Similarly, studies have demonstrated that administering PPARy agonists reversed memory impairments in experimental models of AD (Escribano et al., 2010, 2009; Nicolakakis et al., 2008; Papadopoulos et al., 2013; Rodriguez-Rivera et al., 2011). These effects were associated with reduced deposition of AB, thought to be due to

suppression of BACE1 and modulation of phagocytic clearance of AB by microglia (Mandrekar-Colucci et al., 2012; Sastre et al., 2003; Yamanaka et al., 2012).

Mirroring the results from clinical trials in PD, human trial data using glitazones in patients with AD have so far been unsatisfying. Rosiglitazone has previously been tested in populations of AD patients. An initial pilot trial indicated improved recall and attention in patients with mild AD(Watson et al., 2005), and a subsequent phase 2 trial suggested beneficial effects in a subset of APOE e4 non-carrier patients (Risner et al.). However, subsequent phase 3 trials failed to show any evidence of efficacy in any of the AD population(Gold et al., 2010), and also showed no improvement in cognition when used as an adjunctive treatment to acetylcholinesterase inhibitors in patients with mild to moderate AD(Harrington et al., 2011). Similar conflicting data were reported in trials of pioglitazone in populations of AD. Although an initial pilot trial assessing drug safety did not detect any efficacy on measures of cognition(Geldmacher et al., 2011), two small trials did suggest beneficial effects on cognition(Hanyu et al., 2009; Sato et al., 2011). However, due to the small numbers of patients and methodology used, proof of efficacy cannot be inferred from these results, but it is interesting that the seemingly positive results occurred in populations of AD patients with co-existing DM.

Possible explanations for this “failure to translate” despite a wealth of promising pre-clinical data may be due to pioglitazone’s inherent poor brain penetrance (Maeshiba et al., 1997). Pioglitazone (and rosiglitazone) are substrates of P-glycoprotein (P-gp), a primary drug efflux transporter present at the blood-brain-barrier (BBB), and recent studies have shown it may act as a stereoselective barrier to significantly limit the entry of pioglitazone (and to a greater extent rosiglitazone) into the brain (Chang et al., 2015). Chronic neuroinflammation, and exposure to pro-inflammatory cytokines such as TNF-alpha increase expression of P-gp(Bauer et al., 2007) and as this is shown to occur in PD (and also AD), it is speculated that this may limit the entry (and any subsequent beneficial effects) of the glitazones into the brain. Also, the majority of pre-clinical data indicates that pioglitazone has maximal neuroprotective effects when administered prior to the onset of neurodegeneration and only partially confers protection after established lesions. In a rat model utilising bilateral 6-OHDA-induced lesions in which over 70% of DA neurons were lost, pioglitazone failed to demonstrate any protective effects(Laloux et al., 2012), with researchers inferring that this was possibly due to the severity of the

damage, leading some to suggest that thiazolidinediones may have limited efficacy in already symptomatic patients.

Additionally, its future potential as a treatment in PD may be limited by adverse cardiovascular effects, an increased risk of fractures and an association with the development of bladder cancers, which already limit its use among diabetics(Azoulay et al., 2012; Consoli and Formoso, 2013; Ferwana et al., 2013; Suzuki et al., 2010). No further trials using glitazones in a PD population are currently planned, but a 5 year, phase 3 trial involving 5000 patients with mild AD is currently underway to further assess the efficacy of pioglitazone as a disease modifying therapy (Clinical trials.gov identifier NCT01931566).

Despite the failure of recent clinical trials and the potential risks associated with this class of drugs, promising in vivo data highlights the need for an improved understanding of the factors influencing pioglitazone's potential for treating PD (and also AD). Recent studies have showed that administering pure stereoisomers of pioglitazone achieved significantly higher brain penetrance than usual racemic formulations, theoretically allowing lower doses to be administered to patients (and thus lowering the risk of side-effects) and also have comparable inhibitory effects on AB deposition(Chang and Ho, 2013; Chang et al., 2015). Also, following the discovery that the insulin sensitizing effects of pioglitazone may occur independently of PPARy(Grahame Hardie, 2014; LeBrasseur et al., 2006), and its mitochondrial enhancing effects may involve binding directly to complexes on the inner mitochondrial membrane (identified as mTOT (mitochondrial target of thiazolidinediones)) (Colca et al., 2004; Jerry R Colca et al., 2013), novel compounds that activate similar pathways but are "PPAR-sparing" are in early development in testing against models of PD, which may offer similar benefits of neuroprotection with limited side effects(J R Colca et al., 2013).

6.4 Glucagon-like Peptide-1(GLP-1) analogs

Though structurally unrelated to insulin, glucagon-like peptide-1 (GLP-1) analogs activate signalling pathways that converge on the insulin signalling pathway and facilitate insulin signalling. GLP-1 is one of two hormones responsible for mediating the "incretin" effect (the other being glucose-dependent insulinotropic polypeptide (GIP)). Secreted from L-cells in the small intestine in response to food ingestion, GLP-1 stimulates glucose-dependent insulin secretion, insulin biosynthesis and

slows gut emptying and inhibits glucagon secretion, to mediate glucose homeostasis. In addition to its metabolic effects, it also exerts trophic effects, enhancing islet beta cell proliferation, differentiation, inhibiting apoptosis, and enhancing cell survival, thus regulating beta-cell mass (Drucker et al., 2010; Lovshin and Drucker, 2009). Unfortunately endogenous GLP-1 is rapidly rendered inactive by circulating enzyme dipeptidyl peptidase 4 (DPP-IV) within 2 minutes (Drucker, 2003; Kieffer et al., 1995) (Holst et al., 2011) into a metabolite that has no activity against the GLP-1 receptor. However, injectable analogs which are resistant to DPP-IV have since been developed for use in diabetes (such as exenatide, liraglutide, lixisenatide and dulaglutide) which act as long acting agonists to the GLP-1 receptor and exert a dose-dependent pharmacological effect, equivalent to that of raising circulating levels of endogenous GLP-1 levels by eightfold (Gentilella et al., 2009).

Similar to insulin, 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 which project to cortical, hypothalamic and hippocampal nuclei. GLP-1, in its role as a neuropeptide, can diffuse within the brain to regulate many autonomic and neuroendocrine functions including promoting satiety, pancreatic secretions, slowing gastric emptying and regulation of blood pressure and heart rate (Heppner et al., 2015). GLP-1's actions are mediated by the GLP-1 receptor, a 7-transmembrane spanning G-protein coupled receptor (GPCR), which, though 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 (Alvarez et al., 2005). Similar to islet cells that can up regulate GLP-1 expression under stressful conditions such as T2DM (Habener and Stanojevic, 2013), it has also recently been discovered that microglial cells can also increase GLP-1 and GLP-1R expression in response to inflammatory stimuli (Kappe et al., 2012), suggesting GLP-1 may be a natural response to limit harmful stimuli.

Following binding of GLP-1 and activation of the alpha subunit of the GPCR, adenyl cyclase is activated leading to an increase of intracellular cyclic adenosine monophosphate (cAMP). This leads to activation of protein kinase A (PKA), which phosphorylates and activates a variety of downstream signalling molecules involved in promoting cellular survival (Baggio and Drucker, 2007). This results in the activation of a number of important signalling cascades which can be simplified into two main branches - the PI3K-AKT and MAPK pathways (the same pathways that become inactivated during

insulin resistance). Activation of these pathways, as described above, are involved in phosphorylating several downstream effectors that modulate multiple processes including protein synthesis, promoting axonal growth and cell survival, enhancing mitochondrial function, and inhibition of cell apoptosis and inflammatory cascades. Due to the number of cellular processes these influential pathways modulate, it is perhaps not unsurprising that GLP-1 stimulation can modulate functions that become disrupted in PD. A growing number of studies show that GLP-1 receptor stimulation can act a neurotrophic factor(Perry et al., 2002), enhance mitochondrial biogenesis(Kang et al., 2014), inhibit apoptosis(Li et al., 2009), and inhibit inflammatory cascades and reduce oxidative stress(Li et al., 2013), and have subsequently shown neuroprotective properties across a range of experimental models of PD.

Exenatide was the first GLP-1 analogue derived from exendin-4, a naturally DPP-IV resistant peptide discovered in the saliva of the Gila monster (*Heloderma suspectum*) and has demonstrated neuroprotective and neurorestorative properties in a range of experimental models of PD. Administration of exenatide to rodent models of PD halted 6-OHDA and MPTP-induced dopaminergic degeneration (toxins leading to mitochondrial dysfunction, oxidative stress and microglial activation), restored dopaminergic imbalance, and led to persistent improvements in motor function. These effects were accompanied by an increase in the number of TH/VMAT2-positive neurons in the substantia nigra, suggesting an enhancement of neurogenesis (Bertilsson et al., 2008; Harkavyi et al., 2008; Li et al., 2009). Similarly, in rodent lipopolysaccharide and MPTP models of PD, exenatide completely attenuated and reversed the established nigro-striatal lesions, accompanied by reduced microglial activation and supressed production of pro-inflammatory cytokines. This resulted in functional improvements in behaviour and significantly reduced apomorphine-induced circling(Harkavyi et al., 2008; Kim et al., 2009). Interestingly, exenatide was also able to reverse neuropsychiatric dysfunction and restore dopamine, noradrenaline and serotonin content in a novel rodent model with noradrenergic and serotonergic deficits(Rampersaud et al., 2012). Recently, newer GLP-1 analogs based on human GLP-1 have been developed with longer half-lives such as liraglutide and lixisenatide and have also demonstrated neuroprotective effects and improved motor function in the MPTP rodent model of PD(W. Liu et al., 2015).

In clinical trials, exenatide exposure in a small, open label RCT in 45 PD patients led to a mean advantage of 7.0 points on the MDS-UPDRS Part III in the exenatide group, 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 (Aviles-Olmos et al., 2014, 2013a).

GLP-1 analogs also have demonstrated significant effects on AD-related pathology and cognition. In rodent models of AD, GLP-1 analogs have been shown to reduce deposition of AB, and AB-induced pro-inflammatory responses, enhance synaptic plasticity, hippocampal neurogenesis and LTP, and reduce cognitive deficits(Gengler et al., 2012; Hamilton et al., 2011; Han et al., 2013; Y. Li et al., 2010; McClean et al., 2010; McGovern et al., 2012; Perry et al., 2003; Porter et al., 2010; Wang et al., 2010).

In parallel with encouraging results from the small PD trial, data from a double-blind, RCT assessing the effects of liraglutide on cerebral amyloid deposits in AD patients have recently been reported. Results suggested that liraglutide treatment halted decline of cerebral glucose metabolism compared with controls – suggesting an ability to stabilise energy metabolism in areas of the brain that have been shown to correlate with cognitive decline in patients with AD (Gejl et al., 2016).

Despite the wide range of beneficial effects seen in models of PD (and on AD-related pathology), mechanistic uncertainty remains regarding the underlying neuroprotective effects (Athauda and Foltynie, 2016). However studies using GLP-1 analogs in models of AD may shed some light on its protective mechanisms. In view of the fact that increased levels of phosphorylated IRS-1 has been identified as the primary cause of neuronal insulin resistance in AD, (and have also been implicated in PD) exenatide and liraglutide have also demonstrated the ability to reduce levels of IRS-1 pS616 and IRS-1 pS36 in the APP/PS1 model of AD and diabetic mice. This has been shown to not only lead to facilitation of insulin signalling, but the restoration of normal tissue responses to insulin (Bomfim et al., 2012; Long-Smith et al., 2013; Ma et al., 2015), resulting in improvements in AD pathology and functional improvements in cognition. These beneficial effects on neuronal insulin resistance and restoration of insulin signalling essentially restores and increases the basal activation of the AKT pathway, activating signalling cascades that ultimately promote cellular survival. Though not yet

confirmed in PD, it may be tempting to speculate similar mechanisms underlie some of the beneficial effects seen in PD.

Regardless of whether their useful mechanism of action in neurodegeneration is via an insulinotropic effect, or via an effect on IRS-1 phosphorylation, or via GLP-1 receptor action on AKT, in regards to the potential utility of this class of drugs in PD, these drugs are generally well tolerated. Gastrointestinal side-effects and weight loss are common, but due to the glucose-dependent nature of its effects in insulin secretion, the risk of inducing hypoglycaemia in a non-diabetic population is low (Consoli and Formoso, 2015). Although exenatide has been linked to a small increased risk of pancreatitis in patients with diabetes, subsequent meta-analysis has not supported any increased risk (Azoulay et al., 2016)

While the clinical trial data regarding exenatide is encouraging, due to the open label nature of the trial, it should not be interpreted as proof of efficacy in PD, and a larger, double blind trial using a once weekly, long acting form of exenatide in moderate stage PD has recently been completed with results awaited.(Clinical trials.gov Identifier NCT01971242). In parallel, a phase 2 trial evaluating exenatide in 230 patients with AD or MCI (NCT01255163) is currently underway and a randomized, placebo-controlled phase 2 trial assessing the safety and efficacy of liraglutide in 206 patients with early AD (NCT018430755) are continuing.

With the exception of dulaglutide, these peripherally administered drugs are all able to penetrate the blood brain barrier to some degree in experimental models (Hunter and Hölscher, 2012; Kastin and Akerstrom, 2003) to exert central effects in doses comparable to those used in humans. However, there are significant differences regarding their pharmacodynamic and pharmacokinetic properties and their efficacy in glycaemic control in diabetics(Bergenstal et al., 2010; Buse et al., 2009). Thus it may be reasonable to assume that some may exert greater neuroprotective effects in PD than others, though current comparable data is sparse. A recent study indicated that in comparison to liraglutide and lixisenatide, exenatide was less able to offer protection against MPTP-induced dopaminergic degeneration in a mouse model (W. Liu et al., 2015) (though differences in equivalent dosing were not addressed in the study). Similarly although the current crop of GLP-1 analogs including exenatide, liraglutide and lixisenatide are effective in reducing insulin resistance, newer molecules such as

unimolecular dual GLP-1/Gastric inhibitory polypeptide (GIP) agonists or triple GLP-1/GIP/glucagon receptor agonists have been shown to have superior efficacy in reducing peripheral insulin resistance compared to conventional “mono” GLP-1 agonists(Finan et al., 2015, 2013) with additional benefits of reduction of adverse GI effects. A novel dual GLP-1/GIP receptor agonist was recently shown to attenuate dopaminergic cell death in an MPTP mouse model of PD (Cao et al., 2016; Ji et al., 2015) and demonstrated a greater degree of neuroprotection from rotenone-induced mitochondrial stress in SH-SY5Y cells in comparison to older GLP-1 analogs (Jalewa et al., 2016). Similar to GLP-1, oxyntomodulin, is a peptide produced post-prandially by L-cells in the small intestine and acts as an endogenous dual agonist of both the GLP-1 R and the glucagon receptor (Pocai, 2012). Due to its short half-life, protease resistant analogs have been developed as potential treatments for diabetes which have since demonstrated protection against MPTP and rotenone induced cell death in models of PD (Jalewa et al., 2016; W. Liu et al., 2015). As a result these newer agents may also deserve to have exploration of their potential effects in PD.

6.5 DPP-IV inhibitors

DPP-IV inhibitors are a newer class of oral anti-glycaemic drugs currently approved for adjunctive therapy in treating T2DM and include sitagliptin, saxagliptin, vildagliptin and linagliptin. Strictly speaking, DPP-IV inhibitors are not insulin sensitizers, but act to slow the rapid inactivation of endogenous GLP-1, leading to a 2 to 3-fold increase in peripheral basal levels of GLP-1(Ceriello et al., 2014; Shannon, 2013) and potentiation of GLP-1 activity. Recently a population-based case control study found a significantly reduced incidence of PD among individuals with a record of DPP-IV use (OR=0.23, CI 0.07-0.73) (Svenningsson et al., 2016).

Vildagliptin and saxagliptin have shown neuroprotective effects in a rotenone rat model of PD (Abdelsalam and Safar, 2015; Nassar et al., 2015). Rats pre-treated with saxagliptin or vildagliptin prior to rotenone injection demonstrated enhanced striatal dopamine synthesis and reduced dopaminergic neuronal loss, resulting in improved motor performance and coordination in a rotarod and open field tests Further histological examination of rats administered saxagliptin or vildagliptin showed evidence of inhibitory effects on neuroinflammation, with evidence of supressed

myeloperoxidase and NF-kB expression and downstream effectors TNF-alpha, iNOS and ICAM-1, with associated reduced oxidative stress markers. These effects were accompanied by reduced apoptosis of dopaminergic neurons with increased expression of BDNF and Bcl-2 with corresponding decreased TNF-alpha and cytochrome-c. However, others have found conflicting results. Rats acutely or chronically pre-treated with supra-maximal doses of sitagliptin (a DPP-IV inhibitor with a substantially longer half-life than saxagliptin) were not protected against MPTP-induced striatal dopaminergic degeneration(Ribeiro et al., 2012).

Similarly, conflicting results are also seen in models of AD. Saxagliptin has been shown to elevate hippocampal GLP-1 levels and halt AB aggregation, tau phosphorylation and improve inflammatory markers, resulting in improvements in memory retention following 3 months of intracerebral administered streptozotocin(Kosaraju et al., 2013). In addition, chronic administration of sitagliptin in Tg AD mice was associated with increased levels of brain GLP-1 and dose dependent reductions in inflammatory markers in the brain and beta APP and AB deposits (D'Amico et al., 2010), accompanied by improvements in memory impairment in contextual fear conditioning tests. These effects were thought to be partially mediated by increases in acetylcholine content of the hypothalamus and adiponectin receptor 1 expression(Sakr, 2013). However, studies in diabetic rats and primary rat cortical neurons have demonstrated negative effects on AD pathology. Sitagliptin administration has been shown to paradoxically increase tau phosphorylation in the hippocampus and increase IRS-1Ser616 levels, suggesting an enhancement of insulin resistance in the brain(Kim et al., 2012).

The mechanisms underlying the possible neuroprotective effects of DPP-IV inhibitors in PD and AD are unclear, however as the principle target of DPP-IV inhibition, activation and potentiation of the GLP-1receptor with subsequent enhancement of the insulin signalling pathway are thought the most likely explanation, although direct inhibition of enzyme DPP-IV (which itself modulates T-cell activation, growth regulation and cytokine production) may also be relevant(Ansorge et al., 2011). In addition other substrates of DPP-IV exert neuroprotective effects (Matteucci and Giampietro, 2015) and a recent study demonstrated that the neuroprotective effects of linagliptin in a mouse model of focal ischaemia occurred independently of the GLP-1 R (Darsalia et al., 2016), suggesting a further exploration of alternative mechanisms is needed.

No clinical trials of DPP-IV inhibitors in PD (or AD) have yet been undertaken, and in the context of the conflicting data, extrapolating the more positive results seen in animal models to humans may be difficult. Furthermore, the doses of DPP-IV inhibitors used in these animal models are equivalent to 10-20 times higher than those used in the treatment of T2DM, and as such, the high levels of brain GLP-1 in rats produced by DPP-IV inhibition may be difficult to reproduce in humans. Similarly, DPP-IV inhibitors have low penetration of the blood brain barrier, which may be a further limitation compared to GLP-1 agonists (Baggio and Drucker, 2007).

6.6 Metformin

Metformin is an orally active biguanide currently used as a first-line treatment for T2DM and is also classed as an insulin sensitizer. Although it does not stimulate insulin secretion directly (and thus does not induce damaging hypoglycaemia), it exerts its primary glucose lowering effects by inhibiting hepatic gluconeogenesis. Recent evidence suggests it may also be neuroprotective in PD. A cohort study demonstrated that patients with Type 2 diabetes in a Taiwanese population had an almost 2-fold increased incidence of PD, which was exacerbated by the use of sulfonylureas, but the risk was avoided by the use of metformin therapy(Wahlqvist et al., 2012)

Although the underlying mechanism of its metabolic actions relevant to neurodegeneration remains uncertain, its anti-glycaemic effects are thought to be partially dependent on the ability of metformin to activate a duodenal 5′-AMP-activated protein kinase (AMPK)-GLP-1R-PKA dependent neuronal pathway(Duca et al., 2015; Pernicova and Korbonits, 2014). By inhibiting mitochondrial respiratory chain complex I, metformin raises the AMP/ATP ratio, causing AMP binding and activation of AMPK, which is usually downregulated in adipose tissue of obese, insulin resistant individuals, and associated with increased oxidative stress and markers of inflammation(Ruderman et al., 2013). Consequently agonism of AMPK is also thought to underlie metformin's effects in restoring peripheral insulin resistance in patients with T2DM, via modulation of lipid metabolism(Knowler et al., 2002)(Kumar and Dey, 2002). However, recently it has been shown that metformin also can enhance peripheral GLP-1 secretion through cross talk between the upstream insulin and Wnt signalling pathways, and that this may also contribute to its insulin sensitizing effects(Kim et al., 2014).

AMPK acts as a crucial energy sensor in all cell types, including neurons, and regulates whole-body metabolism, being activated after increased ATP demand or metabolic stresses (such as ischaemia, hypoxia, mitochondrial dysfunction or increased intracellular calcium) and improves cellular stress resistance through stimulation of FoxO/DAF-16, Nrf2/SKN-1, and SIRT1 signalling pathways. Furthermore, through mTOR and ULK1 signalling, AMPK also modulates autophagy and protein degradation. In view of its role in numerous cellular processes, perhaps not unsurprisingly, dysregulation of AMPK has been implicated in many neurodegenerative diseases(Liu and Chern, 2015) and has been identified as a possible target for modulation in PD. Growing evidence suggests AMPK acts as a pro-survival factor in models of PD (Choi et al., 2010), and in rodent models, metformin can cross the blood brain barrier and activate AMPK in the CNS(Nath et al., 2009), and has been shown to rescue dopaminergic dysfunction and mitochondrial abnormalities in Drosophila models of PD(Ng et al., 2012). Similarly, metformin induced AMPK activation has been proposed to underlie recent studies that demonstrate metformin is able to reduce levels of alpha-synuclein in vitro and in vivo ,possibly via inhibition of downstream mTOR and enhanced PP2A activity and leading to enhanced de-phosphorylation of alpha-synuclein Ser129 (Pérez-Revuelta et al., 2014).

Metformin also has anti-inflammatory and anti-oxidant properties. Studies demonstrate metformin can protect cortical neurons from apoptosis and can rapidly cross the blood brain barrier and inhibit pro-inflammatory mediators including NF-KB and can increase antioxidant activity and BDNF levels in a MPTP-mouse model, resulting in protection of dopaminergic neurons from degeneration (Patil et al., 2014).

Interestingly, a recent study proposed an alternative mechanism to explain the multitude of neuroprotective effects of metformin. In diabetic and HFD fed mice, chronic metformin administration was able to halt dopaminergic death triggered by the induced metabolic dysfunction by restoring levels of parkin, PARIS and PGC-1a (Khang et al., 2015).

Metformin has also been shown to have beneficial effects on AD-related pathology in multiple experimental models. In diabetic mice and Neuro-2a cell lines, in which insulin resistance induces the development of AD-associated neuropathological changes, metformin re-sensitized the impaired response to insulin and halted the appearance of AD-neuropathology by inhibiting hippocampal tau

phosphorylation, AB generation and JNK activation(Gupta et al., 2011; Jiejie Li et al., 2012). These effects are thought to be mediated via AMPK-activation associated regulation of APP processing, or inhibition of mTOR and subsequent activation of PPA2 resulting in promotion of autophagy of AB and dephosphorylating tau protein.

No clinical data examining the use of metformin in populations of PD patients yet exists, but a study examining the effects of metformin on patients with PD is currently in the planning stages. In parallel, a pilot study using metformin to examine the effects on cognition and biomarkers of patients with MCI and dementia due to AD is currently underway (Clinical trials Gov NCT01965756).

While clinical studies show that metformin is a safe, generally well-tolerated drug in an elderly population(Kosmalski et al., 2012), and therefore of potential use in the treatment of a PD population, there is conflicting data regarding its effects on cognition and AD-related pathology. Previous studies have suggested metformin may actually exacerbate AD-related neuropathology, which, given the interaction with alpha-synuclein, may be detrimental to patients with PD. While some epidemiological data suggests that patients with T2DM using metformin reduce the risk of dementia by 35%(Hsu et al., 2011), others indicate that chronic users of metformin actually had a higher risk of developing AD than those who were not on the drug(Imfeld et al., 2012). Similarly, pre-clinical studies have shown that metformin can exacerbate intra- and extra-cellular production of AB, possibly via the AMPK-dependent transcriptional upregulation of BACE1(Chen et al., 2009). In parallel with this are studies that indicate that over or chronic activation of AMPK in models of AD(Ma et al., 2014; Mairet-Coello et al., 2013), ALS(Y.-J. Liu et al., 2015b)(Y.-J. Liu et al., 2015a) and HD(Ju et al., 2011)(Ju et al., 2014) are associated with detrimental effects. Furthermore, the responsiveness of AMPK declines with age(Salminen and Kaarniranta, 2012), and it may well be that in PD, as in experimental models of stroke, in which the protective or detrimental effects of AMPK activation are dependent on age and duration of AMPK activation(J. Li et al., 2010), metformin may be a mixed blessing in regards to effects on PD (and AD) related pathology.

6.7 Novel compounds

While repurposing current anti-glycaemic drugs is an important route to potentially rapid and new treatments for PD, several “off-target” effects often cause adverse effects that may limit use, and

therefore novel molecules that selectively target defective inulin signalling may ultimately prove to be more efficacious. For example, protein tyrosine phosphatase-1B (PTP1B) is a negative regulator of insulin and leptin signalling, dephosphorylating specific phosphotyrosine (pTyr) residues on the insulin receptor and on insulin receptor substrate proteins, and novel compounds that act as PTP1B inhibitors have been shown to significantly improve peripheral insulin resistance and insulin action and signalling in hypothalamus(Liu et al., 2010; Picardi et al., 2008), and cross the blood brain barrier to activate the insulin signalling pathway(Qin et al., 2015).Although these compounds are in early stages of testing in diabetes, they potentially could be efficacious in PD.

7. Conclusion

Although the details of the pathogenesis of PD remain to be further defined, a growing body of evidence links insulin resistance to PD and while the underlying mechanisms remain unclear, there is accumulating evidence suggesting that alpha-synuclein can interfere with normal insulin signalling, via its action on inflammation and the AKT pathway. The downstream consequences may further exacerbate alpha synuclein oligomer formation and protein aggregation. Encouragingly, studies show that the loss of insulin's pleotropic effects in models of insulin resistance and the resultant exacerbation of PD pathology can be somewhat counteracted by restoring or stimulating this pathway using anti-diabetic drugs. Although GLP-1 analogs have been shown to cross the blood brain barrier and activate GLP-1 receptors in experimental models of PD, it remains to be seen whether the resultant positive effects on PD are mediated centrally, peripherally, or via a combination of both. The question also remains whether the resultant neuroprotective effects seen in pre-clinical models by targeting this novel pathway will translate to detectable disease modification but initial data from human trials are encouraging.

The current mainstay of managing cognitive decline is aimed at augmenting depleted neurotransmitter deficits and only one drug, the acetylcholinesterase inhibitor rivastigmine, is licensed for treatment in PDD and DLB. Although there is supportive evidence for positive effects on cognition and behavioural disturbances, its use can often be associated with worsening motor deficits and it does not affect the underlying progressive nature of degeneration. Growing evidence also links insulin resistance with cognitive decline and evidence of neuronal insulin resistance has also recently

been linked with DLB. Given that cognitive decline in PD not only encompasses abnormal deposition of alpha-synuclein, but also interacts with pathology typically found in AD, strategies that aim to target AB and tau may also become increasing relevant in attempting to halt cognitive decline. In parallel, links between insulin resistance and AD are growing, and anti-diabetic drugs have also shown great promise in inhibiting the spread of AD-related pathology in pre-clinical studies, while initial efforts at restoring insulin signalling in humans with insulin have translated to significant clinical improvements(Craft et al., 2012). Although PD and AD encompass two separate pathologies, given their apparent inter-relatedness, there may be a role for this class of drugs in ameliorating cognitive decline in at least a subset of PD patients also.

Despite the promising early data, there may be some caveats. Computational models combining PD and insulin resistance indicate that early correction or restoration of insulin resistance would seem to offer the most maximal effects(Braatz and Coleman, 2015), and in parallel, it appears that the timing of when to instigate these drugs appears crucial. Studies in AD indicate that neurons become increasingly insulin resistant during the disease process, and also reveal that PPARy is downregulated in ageing mice compared to young mice(Escribano et al., 2009). In addition, a recent study showed that early intervention with GLP-1 analogs could prevent age-dependent tau hyperphosphorylation in mice while insulin administration could not (Ma et al., 2015), suggesting that there may be, as yet to be ascertained disease-stage and drug specific therapeutic windows. The first clinical trials utilising GLP-1 agonists in PD are currently underway and the results are eagerly anticipated.

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