Multiple avenues of research including epidemiology, molecular genetics and cell biology have identified links between Parkinson’s disease and type 2 diabetes mellitus. Several recent discoveries have highlighted common cellular pathways that potentially relate neurodegenerative processes with abnormal mitochondrial function and abnormal glucose metabolism. This includes converging evidence identifying that peroxisome proliferator activated receptor gamma coactivator 1-α, a key regulator of enzymes involved in mitochondrial respiration and insulin resistance, is potentially pivotal in the pathogenesis of neurodegeneration in Parkinson’s disease. This evidence supports further study of these pathways, most importantly to identify neuroprotective agents for Parkinson’s disease, and/or establish more effective prevention or treatment for type 2 diabetes mellitus. In parallel with these advances, there are already randomized trials evaluating several established treatments for insulin resistance (pioglitazone and exenatide) as possible disease modifying drugs in Parkinson’s disease, with only preliminary insights regarding their mechanisms of action in neurodegeneration, which may be effective in both disease processes through an action on mitochondrial function. Furthermore, parallels are also emerging between these same pathways and neurodegeneration associated with Alzheimer’s disease and Huntington’s disease. Our aim is to highlight this converging evidence and stimulate further hypothesis-testing studies specifically with reference to the potential development of novel neuroprotective agents in Parkinson’s disease.

Keywords: Parkinson’s disease; type 2 diabetes; neuroprotection; Alzheimer’s disease

Abbreviations: PGC1α = peroxisome proliferator activated receptor gamma coactivator 1 α; MPTP = 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine; PINK1 = PTEN-induced putative kinase 1; PARIS = parkin interacting substrate

Introduction

The pathogenesis of Parkinson’s disease is gradually being elucidated through the combined efforts of epidemiologists, geneticists and molecular and cell biologists. Overlapping and interrelated pathways involving mitochondrial turnover (mitophagy and mitochondrial biogenesis), neuroinflammation and aggregation and disaggregation of toxic protein oligomers, all appear to be contributory. While these discoveries represent clear progress, from the patient’s perspective, there remains a greater urgency to search for and test potential neuroprotective or even neurorestorative treatments even prior to a definitive understanding of disease pathogenesis.

Important steps in this neurodegenerative pathway have recently been discovered highlighting links between Parkinson's disease pathogenesis and the mechanisms underlying the development of
insulin resistance. This is particularly noteworthy since several agents used in the treatment of type 2 diabetes have been shown to be neuroprotective in animal models of Parkinson’s disease and are now being evaluated in randomized controlled trials in patients with Parkinson’s disease. This review provides a synthesis of the emerging links between Parkinson’s disease pathogenesis and insulin resistance to generate hypotheses that can be further confirmed or refuted, and to describe the basis for the investigation of anti-diabetes agents as possible neuroprotective agents in Parkinson’s disease.

Search strategy

References for this review were identified through searches of PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) with the search terms: Parkinson’s disease, neurodegeneration, diabetes, insulin resistance, mitochondrial, PGC1α, pioglitazone and exendin-9 from 1990 to May 2011. Articles were also obtained through searches of the author’s own files. Only papers published in English were reviewed. The final reference list was generated on the basis of relevance to the broad scope of this review.

Links between Parkinson’s disease and type 2 diabetes mellitus

Epidemiology

Evidence from prospective epidemiological studies has identified type 2 diabetes mellitus as an independent risk factor for multiple diseases of the nervous system such as diabetic neuropathy (Boulton et al., 2005), stroke (Tuomilehto et al., 1996; Hu et al., 2006) and more recently Alzheimer’s disease (Leibson et al., 1997; Ott et al., 1999; Peila et al., 2002). There are also reports of varying associations between diabetes or abnormal glucose tolerance and sporadic forms of Parkinson’s disease from both cross-sectional and cohort studies. Survey data reveal that diabetes is established in 8–30% of patients with Parkinson’s disease, consistently in excess of the prevalence found in non-Parkinson’s disease individuals (Chalmannov and Vurbanova, 1987; Pressley et al., 2003). This might be readily explained by increased detection of hyperglycaemia through additional medical contact/urine/blood tests among individuals with Parkinson’s disease regularly attending hospital appointments. The association is strengthened by reports suggesting that up to 50–80% of patients with Parkinson’s disease have abnormal glucose tolerance when tested (although these figures are from non-contemporary papers and we are unaware of confirmatory data from more recent cohorts) (Barbeau et al., 1961; Elner and Kandel, 1965; Lipman et al., 1974; Sandyk, 1993); however, in a series of 800 patients with Parkinson’s disease, concurrent diabetes was indeed shown to accelerate progression of both motor and cognitive symptoms (Schwab, 1960). In view of the possible confounding effects of Parkinson’s disease treatment, newly diagnosed, never-treated adults with Parkinson’s disease have also been studied and been shown to have reduced insulin-mediated glucose uptake (Van Woert and Mueller, 1971), inhibition of early insulin secretion and long-term hyperinsulinaemia and hyperglycaemia after glucose loading (Boyd et al., 1971). This takes into account the effects of some drugs used to treat Parkinson’s disease, such as levodopa, which induces both hyperglycaemia and hyperinsulinaemia, whereas others (including the ergot dopamine agonist bromocriptine) may increase insulin sensitivity (Van Woert and Mueller, 1971; Sirtori et al., 1972).

Neuropathological studies of patients with Parkinson’s disease have shown that insulin receptors are densely represented on the dopaminergic neurons of the substantia nigra pars compacta (Unger et al., 1991) and loss of insulin receptor immunoreactivity and messenger RNA in the substantia nigra pars compacta of patients with Parkinson’s disease coincides with loss of tyrosine hydroxylase messenger RNA (the rate-limiting enzyme in dopamine synthesis) (Moroo et al., 1994; Takahashi et al., 1996). Indeed abnormal glucose utilization has been specifically shown in the brains of patients with Parkinson’s disease undergoing either magnetic resonance spectroscopy (Bowen et al., 1995) or fluorodeoxyglucose-PET (Hu et al., 2000) demonstrating increased lactate concentrations and glucose hypometabolism, supporting the hypothesis that Parkinson’s disease is a systemic disorder characterized by a derangement of oxidative energy metabolism.

Further evidence for a positive association between Parkinson’s disease and type 2 diabetes mellitus has been obtained from prospective cohort studies. A statistically significant direct association between triceps skinfold thickness and the risk of Parkinson’s disease has been found in the Honolulu Heart Program (Abbott et al., 2002) and both excess weight (Hu et al., 2006) and type 2 diabetes mellitus itself (Hu et al., 2007) were associated with an increased risk of Parkinson’s disease in a population-based prospective cohort of Finnish males and females. This association was independent of the known modifying factors such as smoking status, coffee and alcohol consumption and body weight, tempting speculation regarding common pathways underlying the development of these conditions. Nevertheless, a recent cohort study could not replicate an association between either type 2 diabetes mellitus or obesity and Parkinson’s disease risk although the authors acknowledge that diagnosis of type 2 diabetes mellitus was entirely based on self-report (Palacios et al., 2011).

Hyperglycaemia and dopamine

Any link between Parkinson’s disease and type 2 diabetes mellitus may relate to abnormalities in a common pathway or indirectly as a consequence of chronic hyperglycaemia or hyperinsulinaemia. Animal and in vitro studies have suggested a role for insulin in the regulation of brain dopaminergic activity featuring a reciprocal regulation between the two chemicals (Craft and Watson, 2004). In the rat, elevation of glucose concentrations in the blood, to levels equivalent to those produced by a meal or stress, suppresses the firing of dopamine-containing neurons located within the substantia nigra and prevents or reverses the increase in discharge rates of dopaminergic cells normally elicited by the dopamine-receptor antagonist haloperidol (Saller and Chiodo, 1980). Administration of glucose to rats has also been shown to produce a significant decrease of dopamine turnover in both striatum and olfactory tubercle (Montefusco et al., 1983). Furthermore, hyperglycaemia related to hyposulininaemia resulting from streptozotocin-induced diabetes (which leads to toxicity to β islet cells and is a model of type 1 diabetes mellitus) has been shown to decrease basal dopamine concentrations and amphetamine-
induced dopamine overflow in the mesolimbic cortex (Murzi et al., 1996).

Chronic hyperglycaemia leads to oxidative stress and the production of reactive oxygen species, which has been implicated in the ongoing β cell death in type 2 diabetes mellitus (Evans et al., 2002). While production of reactive oxygen species may also be a mechanism underlying dopaminergic cell loss in hyperglycaemic animals, this remains speculative, and a further possibility emerges from work demonstrating that in both insulin-deficient rats and insulin-resistant mice, diabetes impairs hippocampus-dependent memory, synaptic plasticity and adult neurogenesis (Stranahan et al., 2008, 2010). However, given that any epidemiological association between Parkinson’s disease and dopamine appears restricted to type 2 diabetes mellitus, it is likely that chronic hyperglycaemia per se, is only a minor risk factor for Parkinson’s disease in humans.

**Insulin resistance and mitochondrial dysfunction**

The development of insulin resistance in humans is closely correlated with immune cell infiltration and inflammation, with clear links between the development of obesity, type 2 diabetes mellitus and cardiovascular disease (Hotamisligil, 2006). Unambiguous links have also been established between exercise, obesity, insulin resistance and levels of interleukin-6 (Kern et al., 2001). Evidence for mitochondrial dysfunction in the development of insulin resistance has been obtained through measuring rates of in vivo mitochondrial phosphorylation using proton 1(H) magnetic resonance spectroscopy in the relatives of patients with type 2 diabetes mellitus, finding that rates of mitochondrial ATP production are reduced by 30% in the muscle of lean, pre-diabetic insulin resistant subjects (Petersen et al., 2004). In addition, there are many specific examples of insulin resistance occurring due to mitochondrial mutations; it has been estimated that ~1.5% of type 2 diabetes mellitus is attributable to the mitochondrial A3243G mutation [the cause of mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS; Gerbitz et al., 1995)].

The more widespread development of insulin resistance has also been proposed to be mediated through mitochondrial dysfunction (Stark and Roden, 2007) at least to a partial extent through muscle expression of transcriptional regulators including PGC1α, an important regulator of enzymes involved in mitochondrial respiration. Expression of PGC1α is rapidly induced following even a single bout of exercise, which then reverts to baseline after cessation of exercise to enable fine control of the energy demands of skeletal muscle (Handschin and Spiegelman, 2008). Individuals that undergo regular exercise have chronically elevated levels of PGC1α in association with a switch in muscle fibre type characterized by increased mitochondrial density and function (Lin et al., 2002).

Direct exploration of patterns of gene expression associated with insulin resistance has been studied in skeletal muscle in patients with type 2 diabetes mellitus as well as non-diabetic individuals with and without a family history of type 2 diabetes mellitus. The earliest sign of insulin resistance was shown to be reduction in expression of PGC1α and the mitochondrial gene nuclear respiratory factor 1 (NRF1) (Patti et al., 2003). In a whole genome methylation analysis of skeletal muscle from type 2 diabetes mellitus and control subjects, hypermethylation of PGC1α was found in association with reduced PGC1α messenger RNA and reduced mitochondrial DNA levels in subjects with type 2 diabetes mellitus. Hypermethylation of PGC1α can be induced by dietary factors such as fatty acids, as well as cytokines such as tumour necrosis factor-α (TNF-α), suggesting a potential mechanism underlying the gene–environment interaction in type 2 diabetes mellitus risk (Barrès et al., 2009).

**Parkinson’s disease and mitochondrial dysfunction**

The earliest link between Parkinson’s disease and mitochondrial dysfunction followed the observation that individuals injected with heroin contaminated with MPTP (1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine) acutely developed parkinsonism (Langston et al., 1983). Both MPTP and another environmental toxin, rotenone, were subsequently shown to cause degeneration of dopaminergic neurons in animal models by selective inhibition of complex I (Gerlach et al., 1991) suggesting that in humans, complex I impairment may itself be sufficient to cause the disease. Complex I (NADH CoQ dehydrogenase) is the first enzyme of the mitochondrial respiratory chain, playing a crucial role in ATP generation. Complex I dysfunction decreases ATP production, generates free radicals and sensitizes cells to the pro-apoptotic protein Bax thus leading to apoptosis (Perier et al., 2005). A direct relation between mitochondrial dysfunction and sporadic Parkinson’s disease has been demonstrated in post-mortem tissue, revealing complex I deficiency (Schapira et al., 1989; Mann et al., 1994) and damage (Keeney et al., 2006) in the substantia nigra of patients with Parkinson’s disease. However, it is likely that neurodegeneration provoked by complex I inhibitors alone is rare. Complex I toxins may, however, contribute to the pathogenesis of Parkinson’s disease acting in tandem with other environmental influences and genetic causes (Schapira, 2010). Although also rare, there are numerous reports of parkinsonism occurring in association with mitochondrial mutations including the G11778A mutation associated with Leber’s hereditary optic neuropathy (Simon et al., 1999), polymerase-γ mutations (Luoma et al., 2007) and more commonly in association with somatic mitochondrial deletions (Bender et al., 2006). A common mitochondrial haplotype has also been associated with sporadic Parkinson’s disease (Pyle et al., 2005).

Converging evidence suggests that both environmental and genetic factors can interfere with normal processes of the removal of damaged or dysfunctional mitochondria known as mitophagy. Healthy mitochondrial turnover through mitophagy and mitochondrial biogenesis as well as ongoing processes of fission, fusion and mitochondrial budding are all essential to maintain normal cellular bioenergetic function. This relies on intact mitochondrial DNA, which is particularly vulnerable to damage by free radicals due to its lack of a histone coat and limited facilities for repair.
Furthermore mitochondrial DNA mutations, whether induced by oxidative stress or ageing, have a further effect on complex I and respiratory chain function leading to increased damage again through the production of reactive oxygen species (Cooper et al., 1992). Normal human substantia nigra and striatum exhibit the greatest free radical-mediated mitochondrial damage with age (Kryatsberg et al., 2006). Other cellular pathways essential for normal mitochondrial turnover have been identified directly as a result of the identification of specific gene mutations causing Mendelian forms of Parkinson’s disease (Schipani, 2008).

Parkin mutations cause autosomal recessive juvenile parkinsonism. Intracellular localization studies have reported the association of parkin and mitochondria (Stichel et al., 2000). The function of parkin is not completely clear but the protein has E3 ligase activity, and is thought to monitor the quality of mitochondria and trigger mitophagy of dysfunctional mitochondria (Rakovic et al., 2010), by triggering the ubiquitin–proteasome system (Chan et al., 2011). Parkin knockout mice have demonstrated alterations in abundance and/or modification of a number of proteins involved in mitochondrial function or oxidative stress, with reductions in several subunits of complexes I and IV, and functional assays showing reductions in respiratory capacity of striatal mitochondria isolated from parkin−/− mice. Furthermore, these mice show a delayed rate of weight gain, suggesting broader metabolic abnormalities (Palacino et al., 2004). Mitochondrial function has also been shown to be decreased (complex I and IV activities) in peripheral blood from patients with parkin mutations (Muftuoglu et al., 2004).

PINK1 (PTEN-induced putative kinase 1) mutations also cause autosomal recessive juvenile parkinsonism. The gene encoding PINK1 encodes a 63-kDa protein with an 8-kDa mitochondrial targeting sequence. In health, this protein is imported intact into the mitochondria, where it has been suggested that PINK1 recruits parkin from the cytoplasm to the mitochondria to initiate the process of mitophagy (Vives-Bauza and Przedborski, 2011).

DJ-1 is a 23-kDa protein that is expressed in peripheral tissues and parts of the brain, including the hippocampus, cerebellum, olfactory bulb, striatum, substantia nigra pars compacta and substantia nigra pars reticulata, both in cells bodies and dendrites, localized to the mitochondrial matrix and intermembrane space (Zhang et al., 2005). The deletion or silencing of DJ-1 causes parkinsonism possibly by sensitising cells to oxidative stress, while over-expression of DJ-1 protects cells implying a protective role for the protein (Yokota et al., 2003). Substantia nigra neurons from DJ-1 knockout mice have increased sensitivity to MPTP and oxidative stress (Kim et al., 2005), while cells derived from patients with DJ-1 mutations have abnormal mitochondrial morphology (Ircher et al., 2010). DJ-1 has been shown to associate with the mitochondrial Bcl-XL, an anti-apoptotic protein (Ren et al., 2011).

α-Synuclein (SNCA) mutations can cause autosomal dominant Parkinson’s disease, and α-synuclein is the main component of the pathological feature of Parkinson’s disease—the Lewy body. The pathological features of Parkinson’s disease, can be replicated by simply over-expressing SNCA in transgenic flies (Feany and Bender, 2000) suggesting that one mechanism by which neurodegeneration occurs is through a toxic ‘gain-of-function’. The exact function of α-synuclein remains unknown, and the relationship between SNCA oligomers and aggregates, their degradation by the ubiquitin–proteasome and lysosomal systems and neuronal toxicity requires further work (Wong and Cuervo, 2010). There are nevertheless indications that SNCA affects various mitochondrial pathways (Poon et al., 2005). SNCA co-localizes with cytochrome c forming hetero-oligomers, which can prevent apoptosis, but in the process forms complexes with prolonged peroxidase activity that induces protracted oxidative stress (Bayir et al., 2009). It has also been shown that phosphorylated SNCA (the dominant form in Parkinson’s disease) influences the normal protein–protein interactions including the ‘pull down’ of protein complexes involved in mitochondrial electron transport (McFarland et al., 2008), while over-expression of SNCA leads to the protein entering mitochondria and interfering with mitochondrial function (Devi et al., 2008; Chinta et al., 2010).

Leucine-rich repeat kinase (LRRK-2) mutations can also cause autosomal dominant Parkinson’s disease. This protein has GTPase and kinase domains and study of its interaction with SNCA is ongoing (Greggio et al., 2011). Whether LRRK-2 plays a critical role in determining the phosphorylation status of SNCA remains to be determined, however, it has recently been demonstrated that in the transgenic G2019S mutant LRRK2 mouse, there is age-dependent degeneration of dopamine nigrostriatal neurons together with damaged mitochondria and an increase in mitophagy (Ramonet et al., 2011).

Glucocerebrosidase (GBA) mutations cause Gaucher’s disease and have been identified as a risk factor for Parkinson’s disease even in the heterozygous state (Sidransky et al., 2009). There has been shown to be a bidirectional link such that SNCA inhibits the lysosomal activity of GBA and functional loss of GBA leads to accumulation of SNCA (Mazzulli et al., 2011), potentially explaining the risk of Parkinson’s disease through a positive feedback loop. Other potential mechanisms also include lipid accumulation and impaired mitophagy or mitochondrial trafficking (Westbroek et al., 2011).

In Parkinson’s disease there is therefore ample evidence of mitochondrial dysfunction that includes complex I inhibition, oxidative stress, PINK1 and DJ-1 dysfunction, and an interaction between parkin and PINK1 that influences mitophagy and mitochondrial biogenesis. Complex I inhibition initiated by any of a range of environmental toxins will increase free radical generation, and thus initiate a vicious cycle of events that further impairs mitochondrial function and may enhance any underlying genetic defects and further impair neuronal activity. Neuroinflammation undoubtedly leads to further mitochondrial stress through the production of reactive oxygen species as well as through the activation of microglia and subsequent release of pro-inflammatory cytokines such as nitric oxide and TNF-α (Whitton, 2007; Tansey et al., 2008). This can be readily detected through the identification of activated microglia on imaging (Gerhard et al., 2006) and neuropathology (McGeer et al., 1988). The role of a neuroinflammatory process in Parkinson’s disease is further supported by the association between the human leukocyte antigen locus and Parkinson’s disease risk in a meta-analysis of genome wide studies (Nalls et al., 2011) and the reported beneficial effects of anti-inflammatory agents on risk of Parkinson’s disease (Wahner et al., 2011).
Converging evidence implicating PGC1α

Converging evidence suggests that cellular pathways leading to either insulin resistance or neurodegeneration involve mitochondrial mechanisms. It is well known that mutations in mitochondrial DNA can lead to a wide variety of phenotypes that commonly involve neurodegeneration and diabetes (Hara et al., 1994; Finsterer et al., 2008). However, these mutations do not account for a significant proportion of cases of sporadic Parkinson’s disease. Normal mitochondrial biogenesis, respiration and metabolism of reactive oxygen species requires intact expression of both nuclear and mitochondrial encoded genomes now recognized as being regulated by PGC1α (Lin et al., 2005; Finck and Kelly, 2006; St-Pierre et al., 2006). It has previously been shown that PGC1α has a powerful suppressive effect on reactive oxygen species production, in parallel to its effects in elevating mitochondrial respiration. This occurs through the PGC1α-mediated expression of genes involved in reactive oxygen species detoxification, as well as PGC1α expression that is rapidly induced by these proteins following a single bout of endurance exercise in vivo (Handschin and Spiegelman, 2008). Insulin resistant patients show reduced expression of PGC1α and the mitochondrial encoded gene COX1 (Heilbronn et al., 2007), while reduction in PGC1α-responsive genes has been shown among patients with type 2 diabetes mellitus and their asymptomatic relatives compared with healthy controls (Petersen et al., 2004). Indeed polymorphisms in PGC1α have been associated with an increased risk for type 2 diabetes mellitus in diverse populations (Ek et al., 2001; Hara et al., 2002; Bhat et al., 2007).

PGC1α has also been implicated as having a major role in Parkinson’s disease pathogenesis. Meta-analysis of gene expression data using microarrays has utilized post-mortem brain homogenates to look at gene expression in the substantia nigra pars compacta of patients with confirmed SNCA-positive Lewy body Parkinson’s disease. Robust three tiered analysis from separate genome wide datasets have indicated that ‘gene sets’ involved in mitochondrial electron transport, mitochondrial biogenesis, glucose utilization and glucose sensing were strongly associated with Parkinson’s disease. Included amongst these gene sets were 10 PGC1α responsive genes. Furthermore it was shown that over-expression of PGC1α was able to protect dopamine cell loss induced by the mitochondrial toxin rotenone (Zheng et al., 2010).

In parallel with these discoveries was the identification of a zinc-finger protein, parkin interacting substrate (PARIS), which is up-regulated 3-fold in the nigra of patients with not only parkin-related parkinsonism but also sporadic Parkinson’s disease, and is both necessary and sufficient for the neurodegeneration associated with parkin animal models (Shin et al., 2011). The same group further identified that PARIS represses the expression of PGC1α and PGC1α target genes playing an important role in mitochondrial function including NRF1, and the oxidative phosphorylation regulator ATP5b. The site of interaction between PARIS and PGC1α is a sequence that is involved in the regulation of transcripts involved in insulin responsiveness and energy metabolism (Mounier and Posner, 2006). Although other pathways are undoubtedly also relevant, it is clear that parkin, PARIS, PGC1α and NRF1 contribute to the pathogenesis of Parkinson’s disease. Loss of expression of PGC1α controlled genes may therefore be a key link between abnormal mitochondrial function, abnormal glucose utilization and Parkinson’s disease. Hypermethylation of PGC1α during life may follow either genetic or environmental influences that promote accumulation of free fatty acids, TNF-α and ceramides (Summers and Nelson, 2005; Staiger et al., 2006; Barrés et al., 2009), which might then lead to decompensation of mitochondrial bioenergetics and the onset of Parkinson’s disease (Figure 1).

Tissue specificity of mitochondrial dysfunction: parallels between insulin resistance, Parkinson’s disease and other neurodegenerative diseases

There has been considerable speculation regarding the (initially) selective degeneration of dopaminergic neurons in Parkinson’s disease. Dopaminergic neurons in the substantia nigra pars compacta have an incredibly complex structure in terms of axon length and number of synapses (>100 000). Mathematical modelling has shown that neuronal energetic demand rises exponentially with axon structure and arbour complexity. This potentially makes dopaminergic neurons of the substantia nigra pars compacta more sensitive to energetic stress than other types of dopamine or indeed non-dopaminergic neurons (Matsuda et al., 2009; Moss and Bolam, 2010).

There is considerable evidence from epidemiology, neuropathology and functional neuroimaging that also implicates diabetes as a risk factor for cognitive impairment and Alzheimer’s disease (Janson et al., 2004; Luchsinger et al., 2007; Toro et al., 2009). In a study of animal models of double-mutant Alzheimer and diabetic transgenic mice, the onset of diabetes has been shown to exacerbate Alzheimer’s disease-like cognitive dysfunction (Takeda et al., 2010). Excessive energy intake appears to affect cognitive function adversely though oxidative stress, inflammation and impaired cellular stress responses (Pistell et al., 2010; Kapogiannis and Mattson, 2011), mediated via reduced expression and/or activity of mitochondrial proteins and oxidative genomic damage (Bishop et al., 2010). In animal models in which neurotoxicity is mediated by oxidative stress, dietary energy restriction has been shown to protect neurons and synapses (Guo et al., 2000), while exercise has been shown to enhance hippocampal neurogenesis and reduce glucocorticoid levels (Kannangara et al., 2010).

Ageing and chronic hyperinsulinaemia both upregulate genes for inflammatory/immune pathways and downregulate insulin signalling genes, blocking glucose utilization and decreasing mitochondrial function in hippocampal neurons (Blalock et al., 2010). This is reflected in the reduction in the activity of several mitochondrial enzymes (e.g. pyruvate and isocitrate dehydrogenases,
Abnormal distribution of mitochondria in fibroblasts taken from subjects with Alzheimer’s disease has been proposed as evidence that mitochondrial fission/fusion processes may have relevance in Alzheimer’s pathogenesis (Wang et al., 2008). Furthermore, there are data to show an association between reduced PGC1α levels and Alzheimer pathology in post-mortem human brains, and that PGC1α over-expression can reduce hyperglycaemia-mediated β amyloidogenesis (Qin et al., 2009).

In parallel with the complexity of nigro-striatal neurons, hippocampal pyramidal neurons have the highest energy requirements of any neurons in the brain (LaManna and Harik, 1985) and this may also contribute to their vulnerability to neurotoxicity mediated via mitochondrial dysfunction in Alzheimer’s disease. Analogous with Parkinson’s disease pathogenesis, it is likely that a combination of factors including amyloid-β oligomer accumulation, oxidative stress as well as a deficit in neurotrophic factor signalling all play a role in mitochondrial dysfunction in vulnerable neurons producing mild cognitive impairment and Alzheimer’s disease (Mattson et al., 2008). The association of molecular alterations in Alzheimer’s disease with perturbed neuronal energy metabolism and the impact of energy intake and expenditure on cognition and ageing suggest an important link between Alzheimer’s disease pathogenesis and brain energy metabolism that may be amenable to pharmacological interventions.

Other neurodegenerative diseases also share links with type 2 diabetes mellitus. Patients with Huntington’s disease develop type 2 diabetes mellitus about seven times more often than matched healthy controls (Podolsky, 1972), and this is a consistent feature in the mouse models of Huntington’s disease (Hurlbert et al., 1999), with ensuing demonstrations that the mutant huntingtin protein has a direct effect on mitochondrial function and trafficking (Orr et al., 2008) and inhibits expression of PGC1α (Cui et al., 2006). In addition, type 2 diabetes mellitus is a common feature of Friedreich’s ataxia, aceruloplasminaemia and ataxia telangiectasia, as well as a range of more esoteric disorders featuring neurodegeneration, reviewed in Ristow et al. (2004).

Therapeutic implications

The converging evidence implicating the PARIS/PGC1α pathway in the neurodegenerative process associated with Parkinson’s disease highlights the need for further study of the therapeutic effects of PARIS inhibition, and/or PGC1α stimulation as potential neuroprotective treatments. High-throughput screens can identify potential compounds for in vitro and in vivo testing ahead of human trials. Particularly exciting is the realization that some of
the existing licensed treatments for type 2 diabetes mellitus potentially have beneficial effects on related pathways of mitochondrial function, directly or indirectly through an influence on PGC1α activity, and trials have already been initiated to evaluate effects on patients with Parkinson’s disease and/or other neurodegenerative diseases.

**Pioglitazone**

Pioglitazone is a licensed treatment for patients with type 2 diabetes mellitus, and reduces insulin resistance via its action on the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ). It modulates the transcription of genes involved in insulin sensitivity. Of major interest is the recent observation that pioglitazone and other active thiazolidinedione compounds bind to the outer mitochondrial membrane protein (mitoNEET) with an affinity comparable to its binding to PPAR-γ, and there has been a suggestion that many of the clinical effects of pioglitazone are mediated by binding to mitoNEET (Colca et al., 2004; Paddock et al., 2007; Wiley et al., 2007). MitoNEET plays a key role in electron transport and oxidative phosphorylation, and pioglitazone binding to MitoNEET has been shown to have positive regulatory effects on complex I activity in neuronal cells (Ghosh et al., 2007).

Pioglitazone has been shown to be protective against neurodegeneration in MPTP mouse models of Parkinson’s disease (Breidert et al., 2002; Dehmer et al., 2004). The neuroprotective properties of pioglitazone have been suggested to be mediated via a sequential action through PPAR activation, inducible nitric oxide synthase induction and nitric oxide-mediated toxicity (Dehmer et al., 2004). Pioglitazone has also been shown to be neuroprotective against the lipopolysaccharide model of Parkinson’s disease through reduction of microglial activation and reduction of oxidative stress, enabling restoration of mitochondrial function (Hunter et al., 2007).

Conflicting data have, however, suggested that the mechanism of action of pioglitazone in protection against MPTP-induced neurodegeneration is solely mediated through the inhibition of monamine oxidase B (MAO-B), which prevents metabolism of MPTP to the toxic MPP+ (Quinn et al., 2008). In view of this uncertainty, but responding to the pressing need to evaluate this agent in patients with Parkinson’s disease, a randomized trial has been initiated to explore possible neuroprotective effects of pioglitazone among patients already on MAO-B inhibitors (Clinical Trials.gov Identifier NCT01280123). Pioglitazone is also being trialled as a treatment for Alzheimer’s disease (Clinical Trials Identifier NCT00982202) and Friedrich’s ataxia (Clinical Trials Identifier NCT00811681).

**Exenatide**

Glucagon-like peptide 1 (GLP-1) is a naturally occurring hormone that has an important role in insulin and glucose homeostasis but has a circulating half-life of only 1–2 min. Exenatide is a synthetic agonist for the GLP-1 receptor and has been granted a license for the treatment of type 2 diabetes with confirmed beneficial effects on glucose control, thought to be mediated by β-cell proliferation, increased insulin production, decreased gluconeogenesis and weight loss that follows chronic GLP-1 receptor stimulation in the gastrointestinal tract (Buse et al., 2004; DeFronzo et al., 2009; Kendall et al., 2005; Drucker et al., 2008). GLP-1 receptors are also distributed throughout the brain and stimulation of central receptors in the hypothalamus is responsible for early satiety. Further effects from central GLP-1 stimulation are as yet unclear, but neurotrophic and neuroprotective properties have been identified in vitro (Perry et al., 2002). Exenatide has been evaluated as a neuroprotective agent in multiple animal models of Parkinson’s disease (Bertilsson et al., 2008; Harkavyi et al., 2008; Kim et al., 2009; Li et al., 2009), demonstrating consistent benefits but again with inconsistent conclusions regarding mechanism of action whether anti-inflammatory (Harkavyi et al., 2008; Kim Chung et al., 2009; Kim et al., 2009) or related to stimulation of neurogenesis (Bertilsson et al., 2008; Belsham et al., 2009; Li et al., 2010). More recently, exenatide has been shown to protect β islet cells from apoptosis, prevent damage to mitochondrial DNA encoded genes and stimulate mitochondrial biogenesis (Fan et al., 2010).

Despite this mechanistic uncertainty (and even encouraged by the potential multiple effects on cell biology) and based on the encouraging data from the animal Parkinson’s disease models, and the excellent safety profile in patients with type 2 diabetes mellitus, recruitment has been completed of patients to a randomized controlled trial at the UCL Institute of Neurology in Queen Square, London evaluating the effects of exenatide on Parkinson’s disease (Clinical trials.gov Identifier NCT01174810).

Scientists and physicians interested in Alzheimer’s disease are also studying the GLP-1 receptor agonists. Exenatide has been shown in animals to promote neuronal activity, enhance synaptic plasticity and cognitive performance (Perry and Greig, 2004). A randomized clinical trial to assess the safety and efficacy of exenatide treatment in participants with early Alzheimer’s disease is currently recruiting participants at NIA (Clinical trials.gov Identifier NCT01255163).

**Conclusions**

A great deal of research has informed on the precise relationships between exercise, obesity, insulin resistance and cardiovascular risk. Links between type 2 diabetes mellitus and widely differing diseases are the subject of increasing interest, aside from the current hypothesis regarding Parkinson’s disease, including possible relationships between diabetes and cancer (Giovannucci et al., 2010). Relationships between insulin, ageing and neurodegeneration have been considered in relation to toxic protein aggregation and the insulin-like growth factor-1 (IGF-1) signalling pathway (Cohen and Dillin, 2008). Alongside the undoubted importance of proteo-toxicity in neurodegeneration, the weight of converging evidence is highlighting the role of impaired mitochondrial function in both Parkinson’s disease and diabetes mellitus, mediated through PGC1α. Therapeutic agents licensed for the treatment of type 2 diabetes mellitus and potentially having an impact on this pathway are already being evaluated in randomized controlled trials of patients with Parkinson’s disease. Further identification of inhibitors and stimulators of the PGC1α pathway in neuronal cells will undoubtedly follow.
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