Ghrelin is neuroprotective in Parkinson's disease: molecular mechanisms of metabolic neuroprotection

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Abstract: Ghrelin is a circulating orexigenic signal that rises with prolonged fasting and falls postprandially. Ghrelin regulates energy homeostasis by stimulating appetite and body weight; however, it also has many nonmetabolic functions including enhanced learning and memory, anxiolytic effects as well as being neuroprotective. In Parkinson's disease, ghrelin enhances dopaminergic survival via reduced microglial and caspase activation and improved mitochondrial function. As mitochondrial dysfunction contributes to Parkinson's disease, any agent that enhances mitochondrial function could be a potential therapeutic target. We propose that ghrelin provides neuroprotective effects via AMPK (5′ adenosine monophosphate-activated protein kinase) activation and enhanced mitophagy (removal of damaged mitochondria) to ultimately enhance mitochondrial bioenergetics. AMPK activation shifts energy balance from a negative to a neutral state and has a role in regulating mitochondrial biogenesis and reducing reactive oxygen species production. Mitophagy is important in Parkinson's disease because damaged mitochondria produce reactive oxygen species resulting in damage to intracellular proteins, lipids and DNA predisposing them to neurodegeneration. Many genetic mutations linked to Parkinson's disease are due to abnormal mitochondrial function and mitophagy, for example LRRK2, PINK1 and Parkin. An interaction between ghrelin and these classic Parkinson's disease markers has not been observed, however by enhancing mitochondrial function, ghrelin or AMPK is a potential therapeutic target for slowing the progression of Parkinson's disease symptoms, both motor and nonmotor.

Keywords: AMPK, calorie restriction, ghrelin, mitophagy, neuroprotection, Parkinson's disease, substantia nigra

Introduction

Parkinson's disease (PD) is a common, debilitating neurodegenerative disease that affects more than 1% of people over the age of 60 and causes a rapidly expanding social, medical and financial burden [Keranen *et al.* 2003]. PD is classically understood to cause progressive motor dysfunction, such as rigidity, resting tremor, postural instability and bradykinesia or slowness of movement, due to the degeneration of dopamine (DA) neurons in the substantia nigra pars compacta (SNpc) that project to the dorsal striatum. The motor symptoms of PD manifest after significant loss of striatal (70–80%) DA concentrations in the brain and are relatively late in the disease progression. The nonmotor symptoms of PD occur before the onset of motor dysfunction and include reduced sleep quality [Zoccolella *et al.* 2011], depression [Starkstein *et al.* 1991], loss of appetite [Politis *et al.* 2010], weight loss [Chen *et al.* 2003] and gastrointestinal disturbances [Edwards *et al.* 1992]. Indeed, the premotor symptoms of PD suggest that the key pathogenic event does not originate within the nigrostriatal DA pathway and that this pathway is uniquely susceptible to degeneration based on earlier primary pathogenic triggers.

Gastrointestinal problems, including delayed gastrointestinal emptying, lack of appetite and difficulty eating are some of the earliest symptoms

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ascribed to PD, suggesting that the primary pathogenic event occurs outside the brain. A pathological hallmark of PD is the accumulation of α-synuclein-positive inclusions in dopaminergic neurons. α-synuclein is a presynaptic protein that is prone to misfolding and aggregates to form Lewy bodies in dopaminergic neurons [Uversky, 2007]. Gene mutations that result in overproduction of α-synuclein lead to early onset PD [Chartier-Harlin *et al*. 2004]. When α-synuclein is overexpressed in both *Drosophila* [Feany and Bender, 2000] and mice [Saha *et al*. 2000] the result is a similar phenotype to human PD, whereby these animals exhibit selective loss of DA neurons, formation of Lewy-body-like inclusions and mitochondrial dysfunction.

There is an emerging line of research that directly examines the link between gastrointestinal tract dysfunction and PD. Braak's hypothesis states that α-synuclein originates from the stomach and migrates into the brain via the enteric nervous system to ultimately reside in SNpc DA neurons [Braak *et al*. 2006] and other central nervous system (CNS) neurons. Indeed, α-synuclein in PD patients accumulates not only in dopaminergic neurons but also in peripheral colon biopsies [Lebouvier *et al*. 2010]. Studies in mice show that α-synuclein overexpression exclusively in gut enteric neurons causes gastrointestinal dysfunction that precedes motor dysfunction [Kuo *et al*. 2010]. Peripheral administration of rotenone results in neurodegeneration of the DA neurons [Alam and Schmidt, 2002] and peripheral low doses of rotenone caused α-synuclein pathology in the enteric nervous system similar to that seen in idiopathic human PD, which resulted in dysfunctional gastrointestinal motility. Intriguingly, Braak's hypothesis suggests that α-synuclein from the gut may be transported and accumulate in the brain. In support of this, several recent studies show that α-synuclein is secreted and can be transported between synaptically connected neurons. In SH5YSY dopaminergic cells and transgenic mice that overexpress α-synuclein there is direct transmission of α-synuclein from these cells to healthy unaffected neurons [Alvarez-Erviti *et al*. 2011; Hansen *et al*. 2011]. In addition, PD patients who received a transplant of fetal mesencephalic dopaminergic neurons develop accumulation of α-synuclein in the grafted neurons [Li *et al*. 2008].

These studies collectively imply that the gastrointestinal system is potentially triggering as well as contributing to the pathogenesis of PD. In addition to the gut/brain neural connection and potential α-synuclein transport along the autonomic nervous system, changes in gut/brain hormonal signaling may underlie or contribute to the pathogenesis and progression of PD. Recent evidence shows that the gut hormones ghrelin and GLP-1 can influence disease progression in PD. This review will focus on the gut hormone ghrelin and its molecular mechanisms in PD.

Ghrelin

It is well documented that calorie restriction can increase lifespan, delay disease onset, and reduce oxidative stress [Colman *et al*. 2009; Qiu *et al*. 2010]. Cultured HeLa cells treated with plasma from calorie restricted rats caused an increase in mitochondrial bioenergetic capacity, mitochondrial biogenesis and reduced reactive oxygen species (ROS) production [Lopez-Lluch *et al*. 2006]. This study indicates that during calorie restriction a component in the plasma, i.e. a circulating factor or hormone, is responsible for the beneficial effects. Ghrelin levels rise significantly during calorie restriction, making it a potential mediator of these effects.

Ghrelin plays a fundamental role in maintaining body weight, blood glucose and adiposity [Andrews, 2011; Sun *et al*. 2008; Tschop *et al*. 2000]. It is predominantly synthesized and released from X/A-like cells of the gastric mucosa the stomach; however, it is also synthesized at many other locations including the pituitary, pancreas and kidney [Gualillo *et al*. 2003]. Ghrelin is synthesized and acylated in the stomach by ghrelin o-acyltransferase (GOAT), which is required for activation of the growth hormone secretagogue receptor (GHSR1a) [Yang *et al*. 2008]. It is then transported to the golgi apparatus where it is cleaved to form the final product ghrelin [Zhu *et al*. 2006]. Both ghrelin and des-acyl (non-acylated) ghrelin are released into the bloodstream [Murakami *et al*. 2002]. The GHSR has two isoforms, GHSR1a and GHSR1b, and acylated ghrelin binds GHSR1a whereas the GHSR1b receptor is not activated by either pharmacological or endogenous ghrelin [Leung *et al*. 2007]. The GHSR1a receptor is constitutively active and studies of reconstituted GHSR1a function on lipid discs shows this is due to intrinsic properties of the receptor protein rather the direct cellular signaling properties and environment [Damian *et al*. 2012]. Administration of

inverse agonists leads to a reduction in receptor internalization, consequently leading to an accumulation on the cell membrane [Holst *et al*. 2004].

Ghrelin is important for meal initiation, as plasma ghrelin levels rise with prolonged fasting and promptly fall postprandially. Ghrelin is well known as a modulator of energy homeostasis; however, it also has many other nonmetabolic functions including enhanced learning and memory through hippocampal synaptic plasticity [Diano *et al*. 2006], anxiolytic effects [Lutter *et al*. 2008] and is neuroprotective in many neurodegenerative diseases including Alzheimer's disease [Gahete *et al*. 2011], amyotrophic lateral sclerosis [Lee *et al*. 2012] and PD [Andrews *et al*. 2009]. When MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which selectively targets dopaminergic neurons in the SNpc to inhibit complex I activity, is administered to mice, there is a reduction in dopaminergic neurons in the SNpc and reduced DA concentration in the striatum. When ghrelin is administered in conjunction with MPTP, ghrelin acts on SNpc neurons to increase the concentration of tyrosine hydroxylase (rate limiting enzyme in the production of DA) in the midbrain as well as DA turnover in the dorsal striatum [Andrews *et al*. 2009]. This study demonstrated that endogenous ghrelin underpinned the neuroprotective effects, as MPTP reduced striatal DA and decreased SNpc DA cell number in ghrelin knockout (KO) compared with wild-type (WT) mice. Moreover, this effect was reversed when the ghrelin receptor was re-expressed selectively on catecholaminergic neurons, showing that ghrelin receptor signaling on catecholaminergic neurons was the primary mode of action. Interestingly, this neuroprotection was dependent upon UCP2, a mitochondrial protein that plays a role in respiration, ROS production, mitochondrial biogenesis and neuroprotection [Andrews *et al*. 2005a, 2005b; Conti *et al*. 2005].

The neuroprotective properties of ghrelin also involve suppressed microglial activation. Microglial activation is associated with phagocytic activity and release of pro-inflammatory cytokines [Banati *et al*. 1993]. Activated microglia accumulate during various neurotoxic insults including trauma [Davalos *et al*. 2005], infection [Rock *et al*. 2004] and neurodegenerative diseases [Dickson *et al*. 1993] in order to remove damaged neurons before they cause any further damage to surrounding healthy cells. Indeed, ghrelin treatment reduced SNpc DA neuronal death with MPTP treatment, and reduced microglial activation [Moon *et al*. 2009]. Burguillos and colleagues recently illustrated that microglial activation is a consequence of apoptotic caspase 8 and 3/7 signaling [Burguillos *et al*. 2011] and ghrelin is known to suppress apoptotic pathways via reduced caspase 3 activation and regulation of Bcl-2 and Bax [Dong *et al*. 2009; Jiang *et al*. 2008]. This reduction in apoptosis occurs in the mitochondria, providing another link between ghrelin and mitochondrial function (Figure 1). Collectively, these studies imply that ghrelin mediates neuroprotective effects by reducing apoptosis and consequent inflammation via reduced caspase-mediated microglial activation, as well as increased mitochondrial biogenesis. Hence, increased circulating levels of plasma ghrelin may provide neuroprotection in PD and reducing plasma ghrelin may predispose individuals to SNpc DA degeneration.

Metabolic status and ghrelin

During calorie restriction ghrelin levels rise and recent studies show that the actions of ghrelin are elevated during negative energy balance, as ghrelin primarily functions to shift an organism from negative to neutral energy balance [Briggs *et al*. 2011]. In addition to promoting food intake after fasting [Salome *et al*. 2009], ghrelin mediates the antidepressive and anti-anxiogenic effects of calorie restriction [Lutter *et al*. 2008], as well as helping to maintain blood glucose during calorie restriction [Zhao *et al*. 2010]. On the other hand, diet-induced obesity suppresses many of the metabolic actions of ghrelin including food intake and growth hormone secretion [Briggs *et al*. 2010; Perreault *et al*. 2004]. These studies imply that metabolic status plays a fundamental role in the effectiveness and actions of ghrelin in the body, whereby negative energy balance enhances ghrelin action and diet-induced obesity attenuates ghrelin action.

Metabolic dysregulation is a risk factor for PD as both obesity and diabetes predispose development of the disease and it is more prevalent in obese patients [Abbott *et al*. 2002], although this correlation with obesity is debated by others [Logroscino *et al*. 2007]. In addition, mouse models of PD show that diet-induced obesity enhances dopaminergic cell loss in a mouse model of PD [Choi *et al*. 2005]. In PD there is a paradoxical

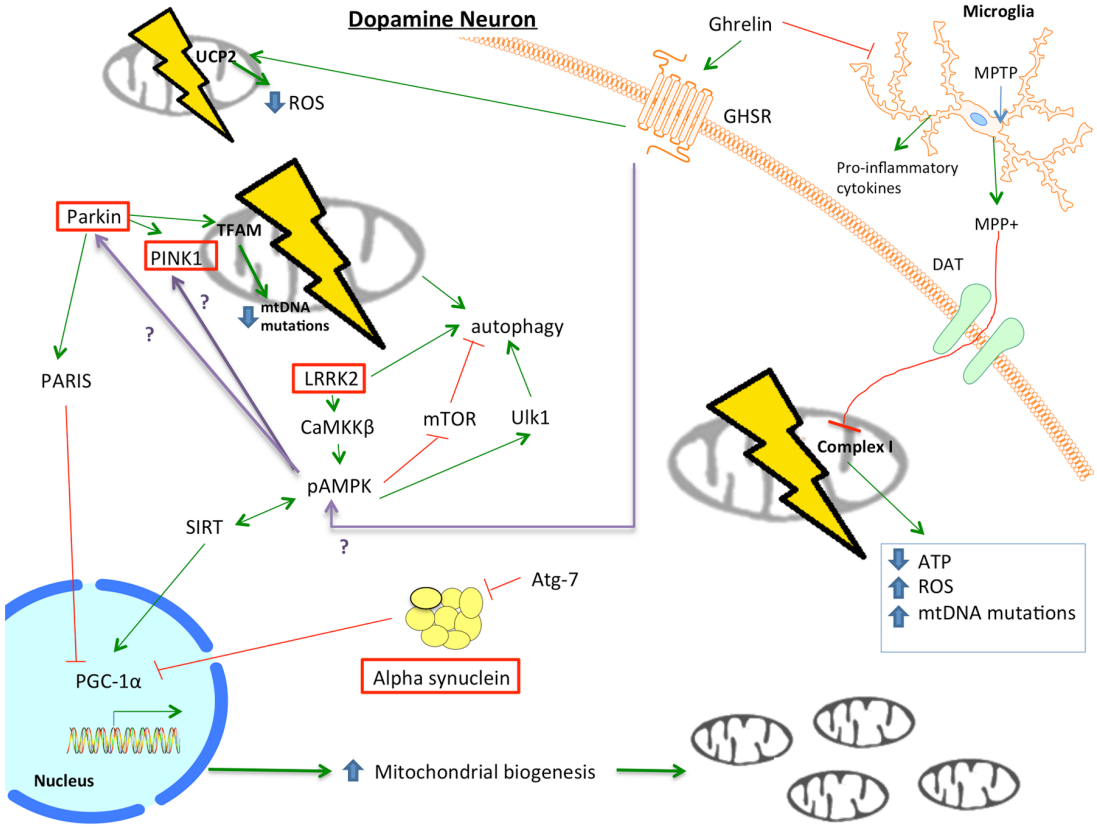

Figure 1. Potential ghrelin neuroprotective pathways in Parkinson's disease. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a model of Parkinson's disease (PD) and recapitulates the disease via inhibition of complex I in the mitochondria resulting in increased oxygen free radicals and reduced adenosine triphosphate (ATP) production. It also acts on microglia by stimulating pro-inflammatory cytokines to enhance the removal of damaged neurons. MPTP crosses the blood–brain barrier and is converted into its toxic form MPP^+, which enters the dopamine (DA) neuron via the dopamine transporter (DAT), making it selective for DA neurons. Ghrelin reduces the inflammatory component of microglial activation observed in PD and also binds to the GHSR receptor to ultimately enhance mitochondrial biogenesis and reduce oxidative stress via UCP2. Ghrelin increases the activity of UCP2 thus reducing reactive oxygen species (ROS) production and oxidative stress. Ghrelin may also act via pAMPK to inhibit mTOR and phosphorylate Ulk1 and enhance autophagy. Dysfunction autophagy, as seen in Atg-7 deficient DA neurons, accelerates a PD phenotype in mice. Other downstream actions of pAMPK involve enhanced SIRT1 activity, to elevate the activity of its downstream target PGC-1α and increase mitochondrial biogenesis. There are many known genetic mutations linked to PD highlighted in red. Many of these are involved in removal of damaged mitochondria, for example the PINK1/Parkin pathway. Damaged mitochondria (depicted with a lightning bolt) attract PINK1 around the damaged organelle. This recruits Parkin from the cytosol and initiates mitophagy. Parkin is involved in reducing mtDNA mutations by enhancing the actions of TFAM and also responsible for maintaining mitochondrial biogenesis by reducing the amount of PARIS in dopaminergic cells. PARIS represses PGC-1α leading to a reduction in mitochondrial biogenesis. Another known gene mutation that results in repression of PGC-1a is alpha synuclein, this is the main pathological hallmark of PD. Any agent that enhances the removal of alpha synuclein is protective in PD, one such example is Atg-7. Another genetic mutation linked to PD is LRRK2 which is responsible for an increase in autophagy and may also interact with AMPK via CaMKKβ. Together this picture illustrates that ghrelin has two main functions: (1) a reduction in oxidative stress via enhanced UCP2 activation and (2) enhanced autophagy; however, it is unknown whether ghrelin, via the action of pAMPK, is connected to enhanced mitophagy via the PINK1/Parkin pathway. Further research will be required to determine whether there is a link.

relationship between plasma ghrelin and body mass index (BMI). PD patients have lower plasma ghrelin concentrations compared to healthy individuals when matched for BMI [Fiszer *et al.* 2010], indicating that ghrelin secretion is disrupted in people with PD. Thus, this evidence suggests that metabolic dysfunction associated with diet-induced obesity contributes to the

progression of PD. Whether deficits in plasma ghrelin signaling in diet-induced obesity predispose individuals to degeneration is unknown.

Ghrelin modulation of the dopamine receptor

In PD, many therapies, such as DRD2 receptor agonists, are used to maintain optimal DA concentration in the striatum. These therapies act directly on dopaminergic neurons and mimic endogenous neurotransmitter resulting in enhanced motor control for PD patients. Any agent that increases the activity of this receptor will reduce motor symptoms associated with PD. Recently the dopaminergic receptor D1R and the ghrelin receptor GHSR1a have shown to physically interact and form heterodimers *in vitro* and show colocalization in the cortex, SNpc, ventral tegumental area (VTA), as well as the hypothalamus [Jiang *et al*. 2006].

To determine the role of GHSR1a:DRD2 heterodimers in appetite Kern and colleagues gave mice cabergoline (DRD2 agonist) [Kern *et al*. 2012]. Selective activation of DRD2 receptors on these neurons resulted in anorexia indicating that activation of DRD2 was sufficient to reduce food intake without the need for ghrelin to be present. This effect was dependent upon the GHSR1a:DRD2 receptor interaction [Kern *et al*. 2012]. Although this study focused on food intake, it indicates that neurons expressing both populations of receptors such as the SNpc, the GHSR1a receptor can modify dopaminergic signaling. Hence, circulating ghrelin can bind to the GHSR1a receptor on DA neurons, form a heterodimer with the DRD2 receptor and enhance DA release in the striatum resulting in reduced motor symptoms in PD. Further, even in the absence of ghrelin ligand binding, GHSR1a and DRD2 could influence signaling and the neuroprotective properties of GHSR1a signaling. Therefore, ghrelin may be neuroprotective in PD by directly activating the GHSR1a receptor to enhance mitochondrial bioenergetics, reduce mitochondrial apoptosis and microglial activation, as well as by modulating the DRD2 receptor to increase DA concentration in the striatum.

Intracellular targets of ghrelin

Determining intracellular targets in PD could potentially lead to new therapeutic strategies to reduce disease progression. When genome-wide analysis was conducted in identified DA neurons from patients with PD, specific gene sets were identified as potential targets. These include defects in mitochondrial electron transport as well as glucose utilization and glucose sensing, all of which are connected to ghrelin. One particular target that was identified was a reduction in peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), [Zheng *et al*. 2010] often referred to as the master regulator of mitochondrial biogenesis. Activation of PGC-1α results in increased mitochondrial number and reduced dopaminergic neuronal loss in the MPTP model [Mudo *et al*. 2012; St-Pierre *et al*. 2006]. Ghrelin, via the action of AMPK (5′ adenosine monophosphate-activated protein kinase) [Andrews *et al*. 2008], increases PGC-1α activation [Canto and Auwerx, 2009]; hence, an increase in ghrelin results in increased PGC-1α leading to enhanced mitochondrial biogenesis. Mitochondrial dysfunction is a well-known contributor to the onset of PD [Abou-Sleiman *et al*. 2006] and mitochondrial interventions may provide a treatment strategy to prevent or reduce neurodegenerative disease progression. A potential target could include PGC-1α or any agent that modulates its activity, for example AMPK (Figure 1). AMPK is an energy sensor that promotes mitochondrial biogenesis to optimize cellular function.

Ghrelin and AMPK

In the hypothalamus ghrelin increases AMPK activity [Andrews *et al*. 2008], whether or not ghrelin increases AMPK in the SNpc is unknown. We hypothesize that ghrelin is neuroprotective in PD via increased AMPK activity in the SNpc (Figure 1). AMPK is a sensor of cellular energy that increases adenosine triphosphate (ATP) production and suppresses energy consumption during cellular stress [Hardie *et al*. 2012]. This includes fatty acid oxidation, increased uptake of glucose and inhibition of fatty acid synthesis [Yamauchi *et al*. 2002]. AMPK increases energy production by regulating mitochondrial function and during chronic energy depletion AMPK is a major regulator of mitochondrial biogenesis in muscle [Bergeron *et al*. 2001]. Consequently, chronic elevation of AMPK by the drug AICAR (acadesine) upregulates key mitochondrial enzymes in skeletal muscle, resulting in mitochondrial biogenesis [Winder *et al*. 2000]. Similar results were observed with β-guanidinopropionic acid (β-GPA), another AMPK activator, in which GPA treatment increased

AMPK activity and mitochondrial biogenesis [Horvath *et al*. 2011]. These beneficial effects of GPA were inhibited by a dominant negative AMPK (DN-AMPK) construct [Zong *et al*. 2002], indicating that elevated AMPK is the main mode of activation. Moreover, exercise is a well-documented physiological stimulus for AMPK activation and aerobic exercise is neuroprotective in PD [Sung *et al*. 2012], suggesting that elevated AMPK could mediate the neuroprotective role of exercise in PD.

Downstream actions of AMPK involve enhanced SIRT1 activity, elevated activity of its downstream target PGC-1α and mitochondrial biogenesis [Canto *et al*. 2009]. PGC-1α levels increase in response to AMPK activity and are also reduced in AMPKα2 KO mice [Iglesias *et al*. 2004]. Further support for the importance of PGC-1α in preventing neurodegeneration comes from PGC-1α null mice, which are more susceptible to MPTP [St-Pierre *et al*. 2006]. Hence, potential intracellular metabolic targets to reduce neurodegeneration include SIRT1, pAMPK and PGC-1α, all of which are activated in response to ghrelin. Recent studies in *Drosophila* support the idea that AMPK mediates the neuroprotective effects of PD. This study used LRRK2 and Parkin null flies to model PD as mutations in either have been linked to early onset PD. Genetic activation of AMPK ameliorated the Parkinsonian phenotype resulting in increased motor control [Ng *et al*. 2012].

AMPK consists of three subunits with different isoforms (α1, α2, β1, β2, γ1, γ2 and γ3) [Carling *et al*. 1994]. Each subunit plays a key role in overall AMPK activity; the alpha subunit has a catalytic role [Crute *et al*. 1998] whereas beta and gamma play regulatory roles. Whole-body deletion of α2 results in mild insulin resistance and impaired glucose tolerance [Jorgensen *et al*. 2004], both these metabolic alterations are features of type 2 diabetes. Furthermore, muscle specific deletion of beta 1 and beta 2 caused mitochondrial dysfunction and insulin resistance [O'Neill *et al*. 2011]. Indeed, activators of AMPK (such as metformin) are well-known treatments of type 2 diabetes and interestingly metformin reduces the risk for developing PD in a population of diabetics [Wahlqvist *et al*. 2012]. As diabetes is a risk factor for PD we believe that AMPK is a promising target for future research in PD.

AMPK is also involved in autophagy, the process whereby damaged or unnecessary organelles (including mitochondria) are removed from the cell. During negative energy balance, AMPK is phosphorylated, resulting in the inhibition of mTOR to ultimately enhance autophagy. AMPK also phosphorylates ULK1 [Kim *et al*. 2011], which is important for the induction of autophagy.

Mitophagy and PD

Problems with mitophagy (the selective degradation of mitochondria) have been linked with PD. Mitochondria are considered the 'powerhouse' of the cell, as they are responsible for aerobic respiration and the conversion of ADP into the energy rich ATP. As mitochondria are essential in maintaining neuronal function and neuronal metabolism, any agent that positively regulates mitochondrial function could be a therapeutic target for reduction or prevention of neurodegenerative disease progression. There are a multitude of mitochondrial impairments that contribute to PD including reduced mitochondrial uncoupling [Andrews *et al*. 2009; Conti *et al*. 2005], increased free radical production and oxidative stress [Lin and Beal, 2006; St-Pierre *et al*. 2006], a reduction in the formation of ATP [Mann *et al*. 1992], impaired calcium buffering [Marongiu *et al*. 2009] and reduced mitochondrial biogenesis [St-Pierre *et al*. 2006].

When mitochondrial dysfunction occurs by any mechanism listed above, damage or loss of cellular function occurs. These damaged mitochondria need to be efficiently removed as otherwise mitochondrial dysfunction results in increased oxidative stress, and damage to DNA, proteins and membrane lipids [Lin and Beal, 2006]. Damaged mitochondria attract PTEN-induced putative kinase protein 1 (PINK1) around the damaged organelle. This recruits Parkin from the cytosol and initiates ubiquitylation of damaged mitochondria [Vives-Bauza *et al*. 2010]. Ubiquitin then binds and labels mitochondria for destruction surrounding it in an isolation membrane. This membrane fuses with lysosomes where mitochondria are degraded and recycled within the cell [Vives-Bauza *et al*. 2010]. Defects in mitophagy result in early onset hereditary forms of PD [Kitada *et al*. 1998]. These defects result from a mutation that leads to loss of function in either PINK1 or Parkin. If mitophagy is affected, damaged mitochondria accumulate, restricting ATP generating potential and increasing ROS production. This decreases neuronal function and predisposes cells to degeneration. Parkin

is also involved in maintaining mitochondrial biogenesis by reducing the amount of PARIS in dopaminergic cells. PARIS represses PGC-1α and the PGC-1α target gene NRF-1 by binding to the insulin response sequence in the PGC-1α promoter. Overexpression of PARIS results in dopaminergic cell death in the SNpc, which is negated when either PGC-1α or Parkin are overexpressed [Shin *et al*. 2011]. This study indicates that Parkin maintains optimal mitochondrial biogenesis via the Parkin–PARIS–PGC-1α pathway. Collectively these studies show that Parkin is responsible for maintaining optimal mitochondrial function and removal of damaged mitochondria via mitophagy.

Removal of damaged components in a cell (autophagy) has been implicated as one factor contributing to the development of PD. Recently, Friedman and colleagues developed a mouse model that is autophagy-deficient by the selective removal of an essential autophagy gene Atg-7. This gene was deleted selectively in dopaminergic neurons, resulting in mice with late onset locomotor deficits similar to those seen in PD. Whole-brain Atg-7 KO results in presynaptic accumulation of LRRK2 and α-synuclein [Friedman *et al*. 2012]. This study implicates disrupted autophagy in the pathogenesis of idiopathic PD. If autophagy is disrupted α-synuclein is allowed to accumulate in cells potentially resulting in the formation of Lewy bodies, a pathological hallmark of PD. In further support of this, mutations in α-synuclein result in early onset PD. α-synuclein also modulates transcription of PGC-1α, the mastergene of mitochondrial biogenesis [Siddiqui *et al*. 2012]. This study shows that nuclear α-synuclein localization is increased under conditions of oxidative stress in vivo and in vitro. Another study using SH-SY5Y cells overexpressing the α-synuclein mutation A53T show that α-synuclein localizes at the mitochondrial membrane resulting in oxidative modification of mitochondrial components [Parihar *et al*. 2008]. These studies indicate that accumulation of α-synuclein during PD will not only disrupt cellular functioning but will also reduce the number of mitochondria present and decrease the likelihood of dopaminergic survival.

Another genetic cause of PD is a defect in the LRRK2 gene where mutations in the LRRK2 gene are associated with both familial and sporadic PD [Bonifati, 2007]. LRRK causes the accumulation of autophagic structures when overexpressed in SY5HSY dopaminergic cells or in transgenic mice [Plowey *et al*. 2008]. LRRK2 also interacts with AMPK via activation of CaMKK-beta resulting in the increase in autophagosome formation [Gomez-Suaga *et al*. 2012]. Following MPTP administration, LRRK2 mRNA levels increase [Hurley *et al*. 2007] and excess LRRK2 accelerates the progression of neuropathic abnormalities such as the formation of Lewy bodies [Lin *et al*. 2009].

In order to overcome mitochondrial pathology such as oxidative stress and defective mitophagy, there is the need to increase mitochondrial turnover. Turnover is enhanced by mitochondrial biogenesis, the process whereby new mitochondria are formed within a cell [Suliman *et al*. 2004]. Enhancing mitochondrial biogenesis represents a therapeutic target for future PD research. We propose that ghrelin via increased AMPK activation will attenuate metabolic degeneration by enhancing mitochondrial biogenesis and turnover, increased autophagy, reduced oxidative stress and potentially may enhance the actions of PINK1, Parkin and LRRK2. The complex relationship between ghrelin, AMPK, PGC-1α, PINK1, Parkin and LRRK2 still remains elusive.

Clinical implications

As PD is a result of reduced DA levels in the striatum the most common option to treat patients is via DA supplementation, i.e. levodopa. However, this pharmaceutical approach is problematic as efficacy diminishes with age and disease severity [Lesser *et al*. 1979]. Levodopa also produces side effects, such as involuntary movements (levodopa-induced dyskinesia), hypotension, gastrointestinal bleeding and nausea [Godwin-Austen *et al*. 1969]. In addition levodopa has been shown to be toxic to DA neurons *in vitro* due to its ease of auto-oxidation, which generates free radicals potentially resulting in oxidative stress [Melamed *et al*. 1998]. As the cause of PD is unknown, therapies that reduce the rate of disease progression or delay disease onset are critically relevant. We believe that alterations in the endogenous regulation of ghrelin contribute to the progression of PD, and that therapies which target the ghrelin system may be of merit in treating both disease progression, and the nonmotor symptoms of reduced appetite, gastrointestinal dysfunction and weight loss associated with PD.

As ghrelin circulates naturally, it is possible to pharmacologically increase the plasma concentration with minimal adverse effects. Patients who have been diagnosed with PD already exhibit reduced levels of circulating ghrelin as well as a reduced postprandial ghrelin response [Unger *et al*. 2011]. Ghrelin may also help to minimize nonmotor effects of PD such as gastrointestinal dysfunction, weight loss and depression, as well as learning and memory deficits [Diano *et al*. 2006; Edwards *et al*. 1992; Starkstein *et al*. 1991]. Nearly all patients diagnosed with PD suffer from selective cognitive impairments, including problems with attention, concentration and memory [Zgaljardic *et al*. 2004] and studies have shown that ghrelin enhances both learning and memory via an increase in synaptic plasticity in the hippocampus [Diano *et al*. 2006]. To date, ghrelin agonists have been successful for the treatment of cachexia to increase food intake and decrease energy expenditure in cancer patients [Neary *et al*. 2004]. These studies indicate that the ghrelin system is a potential therapeutic target to reduce multiple nonmotor symptoms of PD, as well as playing an active role in reducing further neurodegeneration.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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