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Gut Hormones Restrict Neurodegeneration in Parkinson's Disease

Jacqueline Bayliss, Romana Stark,
Alex Reichenbach and Zane B. Andrews
*Department of Physiology
Monash University
Australia*

1. Introduction

Parkinson's disease is the most common neurodegenerative movement disorder and the second most common neurological disorder behind Alzheimer's disease in today's society. It is a progressive disorder that affects more than 1% of people older than 60. Cardinal features of Parkinson's disease include motor dysfunction such as rigidity, resting tremor, postural instability and bradykinesia. These debilitating symptoms manifest due to the massive loss of dopamine in the striatum, the nerve terminal region of dopamine neurons are located in the substantia nigra pars compacta (SNpc). This anatomical circuit is known as the nigrostriatal pathway and plays a critical role in fine tuning motor functions.

At present there are only a few known monogenic mutations accelerating the onset of Parkinson's disease, therefore most cases are considered sporadic and develop as a complex polygenic interaction with age and environment. Although the pathogenesis of Parkinson's disease is largely unknown, mitochondrial dysfunction, oxidative stress, intracellular protein accumulation (Lewy Bodies containing α -synuclein) and abnormal protein degradation all play a key role in disease progression. Because loss of dopamine in the striatum causes motor dysfunction in Parkinson's disease, dopamine supplementation can be used to alleviate motor symptoms but this is only a temporary solution as the efficacy diminishes with age and as the disease progresses. There are no known therapies that halt or reduce the progression of the disease, largely because the cause of Parkinson's disease remains enigmatic.

Parkinson's disease also causes symptoms in other parts of the nervous system. Constipation and gastrointestinal (GI) problems are often some of the earliest symptoms, well before the presence of dopamine dysfunction, and post mortem studies in Parkinson's disease patients identified protein accumulation in the enteric nervous system of the GI tract [1]. This 'Braak's hypothesis' suggests protein accumulation in enteric neurons spreads in a retrograde manner to the brain through the dorsal motor nucleus of the vagus and triggers Parkinson's disease. Braak observed in post mortem tissue that patients with pre-symptomatic Parkinson's disease had protein aggregation in the peripheral nervous system but not the central nervous system [1]. Protein aggregation ascended into the central nervous system and correlated with the development of motor dysfunction. This observation shows that the topographic ascending lesion pattern resembles a falling row of

dominos and prompts the question; does Parkinson's disease originate outside the central nervous system?

Recent evidence supports the hypothesis that GI abnormalities, which precede central nervous system changes, trigger Parkinson's disease. For example, mice expressing mutant α -synuclein in gut enteric neurons exhibited extensive GI dysfunction followed by motor abnormalities [2]. Moreover, low doses of rotenone, a compound found in pesticides that causes Parkinson's-like conditions, produced GI disturbances and enteric neuronal α -synuclein aggregates in rats before neuronal protein aggregation [3, 4]. These studies, taken together with the early GI disturbances in humans, clearly implicate the GI system in the pathogenesis of Parkinson's disease.

The stomach and intestines comprise the GI 'digestive' system, which produces a number of hormones to aid energy metabolism, digestion and nutrient uptake into the circulation. Despite the fact that evidence suggests GI dysfunction triggers Parkinson's disease, little is known about gastrointestinal hormones in Parkinson's disease. This chapter examines how gut hormones influence the nigrostriatal dopamine system.

2. Ghrelin

Ghrelin is best known as a key modulator of energy homeostasis, with critical roles in appetite, adipocyte metabolism and glucose homeostasis [5-7]. These effects are mediated by ghrelin activating the growth hormone secretagogue receptor (GHSR)[8], a seven-transmembrane G-protein-coupled receptor [9] expressed in the brain, heart, lung, pancreas, intestine and adipose tissue [8, 10].

Pro-ghrelin mRNA is highly expressed in the stomach but is also found in the duodenum, jejunum, ileum, colon and pancreas [8]. Pro-ghrelin is acylated in the stomach by ghrelin o-acyltransferase (GOAT) with a medium-chain fatty acid (usually n-octanoic acid) added to serine-3 [11, 12]. Once ghrelin is acylated, it is transported to the golgi apparatus where it is cleaved to form 28 amino-acid mature ghrelin [13]. Both acyl and des-acyl ghrelin are secreted from the stomach into the circulation via the gastric vein [14] with des-acyl ghrelin being dominant in the blood [14].

Within the brain, abundant GHSR expression is found not only in the hypothalamus, reflecting the importance in energy metabolism, but also in many regions outside the hypothalamus [15]. Indeed, the substantia nigra pars compacta (SNpc) houses significant GHSR expression and the GHSR co-localizes with tyrosine hydroxylase (TH) (a dopaminergic marker) neurons, suggesting that ghrelin may play an important functional role in this nucleus. We showed recently that ghrelin binds to dopamine neurons in the SNpc and elicits action potential firing in identified dopamine neurons [16]. Moreover ghrelin increases TH expression (an enzyme involved in dopamine biosynthesis) in the midbrain, and increased dopamine turnover in the dorsal striatum – the innervation site of nerve terminals from dopamine cells in the SNpc [16]. Ghrelin also activates neighbouring dopamine neurons in the ventral tegmental area (VTA) and increases dopamine turnover in the ventral striatum [17], also known as the nucleus accumbens – the innervation site of nerve terminals from dopamine neurons in the VTA. Thus, ghrelin regulates dopamine neuronal function in the SNpc in a manner that suggests a neuroprotective effect against dopaminergic degeneration, as seen in Parkinson's disease.

We used transgenic mice models to show that ghrelin prevents neurodegeneration in SNpc dopamine neurons. For example, using the mitochondrial toxin MPTP, which selective kills

dopamine neurons in the SNpc, we demonstrated that ghrelin knockout mice displayed greater SNpc dopamine cell loss and greater dopamine loss in the striatum. GHSR knockout mice also showed a greater dopamine cell loss in the SNpc and dopamine concentration in the striatum. However, re-expression of the GHSR on dopamine neurons only, using a cre/lox method, completely prevents the greater loss of dopamine neurons in the SNpc and dopamine concentration in the striatum [17]. These results conclusively demonstrate that ghrelin signaling in the SNpc, via the GHSR, restricts SNpc dopamine cell degeneration in mouse models of Parkinson's disease.

Moreover, i.p. ghrelin injection restricts dopamine cell loss in the SNpc and dopamine loss in the striatum *in vivo* [16, 18, 19], providing proof-of-principle data that ghrelin treatment to humans may alleviate symptoms of Parkinson's disease and prevent the development/progression of Parkinson's disease. Ghrelin reduces apoptosis *in vivo* and *in vitro* and attenuates MPTP-induced caspase 3 activity by regulating Bcl-2 and Bax [18, 20]. Bcl-2 and Bax are mitochondrial apoptotic signaling molecules suggesting that ghrelin exerts an influence on mitochondrial function. Ghrelin also reduced microglial activation in the SNpc after MPTP-induced dopamine cell death [19], which participates in the pathogenesis of Parkinson's disease. A recent study shows that apoptosis in degenerating cells produces a caspase-dependent signal that activates microglia [21], therefore it remains unknown as to whether the microglial activation is a direct effect of ghrelin or an indirect effect of greater caspase-mediated apoptotic cell death. However, studies show that ghrelin reduces pro-inflammatory markers such as tumor necrosis factor- α and interleukin 1 β [19], produces anti-inflammatory effects in the periphery [22-24] and in a central hemorrhage model of brain damage [25]. These studies indicate that ghrelin probably has at least some direct effect on microglial activation but also an indirect effect via caspase-mediated signaling [21]. The neuroprotective effects of ghrelin involve enhanced mitochondrial function in SNpc dopamine neurons. For example, ghrelin treatment maintains mitochondrial biogenesis in dopamine neurons after MPTP-induced degeneration [16]. Uncoupling protein-2 (UCP2) is the key mitochondrial target through which ghrelin prevents degeneration. Ghrelin injections restrict dopamine neuronal degeneration after MPTP treatment in UCP2 wild type but not UCP2 knockout mice, highlighting the critical importance of UCP2 to prevent degeneration [16]. The neuroprotective effects of ghrelin on MPTP-induced nigrostriatal dopamine dysfunction included UCP2-dependent mitochondrial respiration, suppression of ROS production and mitochondrial biogenesis [16]. The critical role of UCP2 is supported by previous studies demonstrating that UCP2 is critical for nigrostriatal dopamine function [26] and protects against MPTP-induced degeneration [27-29].

Ghrelin is a hormone that is most well studied for its role in food intake and body weight regulation [6, 7]. Within the hypothalamus ghrelin initiates food intake by activating NPY neurons in the arcuate nucleus [5]. Activation of the ghrelin receptor (GHSR) increases AMPK activity, mitochondrial biogenesis and respiration, and drives food intake [30]. Furthermore, inhibition of AMPK prevents the ability of ghrelin to increase food intake [31]. AMPK is an integrator of cellular energy status and responds to metabolic stress by promoting pathways that favor energy production (fatty acid oxidation, glucose uptake) over energy (ATP) consumption [32]. AMPK activation also promotes mitochondrial biogenesis and function in peripheral and neuronal tissues [33-36], and because of this, we hypothesized that ghrelin mediates neuroprotection in the SNpc by increasing AMPK activity. Indeed, we recently demonstrated that increasing AMPK in the brain prevents MPTP-induced neurodegeneration [37]. We used a dietary approach to chronically activate

AMPK by feeding mice a normal chow diet containing 1% guanidinopropionic acid (GPA) before examining SNpc TH neurodegeneration in a mouse model of Parkinson's disease. GPA is a creatine analogue that inhibits creatine kinase activity, reduces intracellular phosphate levels and thereby robustly increases AMPK activity [33, 38]. Further, GPA stimulates AMPK-dependent mitochondrial biogenesis [35] through increased PGC1 alpha in muscle tissue [39]. In this study we showed that orally administered GPA protects SNpc TH neurons by directly increasing AMPK activity in these neurons. We used design-based stereology to show that GPA regulates TH cell number, cell volume and mitochondrial number and morphology within SNpc TH neurons while decreasing degeneration. In particular, GPA prevented a MPTP-induced decrease of TH cell number in the SNpc and partially retained dopamine levels in the striatum. We speculate that elevated AMPK activity confers the neuroprotective effects of GPA by regulating mitochondrial biogenesis and function. Robust pAMPK staining in TH neurons with and without MPTP indicates that GPA directly enhances AMPK function in SNpc TH neurons. The ability of GPA to activate AMPK in the brain is consistent with previous reports showing that GPA increases AMPK activity in peripheral tissues, such as muscle [33, 35, 40, 41]. Because ghrelin activates AMPK in the hypothalamus to drive food intake and AMPK activity in dopamine neurons reduces degeneration [42], we hypothesize that ghrelin prevents degeneration by increasing AMPK activity in the SNpc. This hypothesis requires further experimental proof.

It is interesting to note that calorie restriction (i.e. negative energy balance) increases plasma ghrelin and calorie restriction has profound beneficial effects on lifespan, neuroprotection, cognition and mood [43-51]. Cultured cells treated with serum from calorie-restricted rats display mitochondrial biogenesis, enhanced bioenergetic capacity and reduced ROS production [52]. These results suggest that the effects of calorie restriction are mediated by a humoral factor affecting mitochondrial metabolism. Indeed, ghrelin levels are increased during calorie restriction in mice, rats and humans [53-57] and ghrelin improved mitochondrial function by regulating ROS, respiration [16, 30], enzyme activity [58] and gene expression [59]. Therefore, ghrelin may underpin many of the enhanced neuronal functions during calorie restriction including neuroprotection [60]. While this hypothesis still needs experimental proof, recent studies support this concept. For example, calorie restriction did not produce a normal anti-anxiety effect in GHSR knockout mice [56] and GOAT knockout mice, which have no acyl ghrelin, were unable to maintain blood glucose levels during calorie restriction. These results show that ghrelin mediates anti-anxiety and glucose homeostasis in calorie restricted mice. Based on this, we hypothesized that ghrelin will mediate the neuroprotective effects of calorie restriction in MPTP mouse models of Parkinson's disease.

In contrast to calorie restriction, plasma ghrelin levels are decreased in obesity in mice and humans [61-63]. Recent evidence also associates obesity with Parkinson's disease in humans [64-66] and obesity is predicted to decrease lifespan in the future [67]. Indeed, obesity increases the susceptibility to MPTP-induced nigrostriatal dysfunction [68], causes reactive gliosis and exacerbates chemically-induced neurodegeneration [69]. Given that ghrelin protects against degeneration in mouse models of Parkinson's disease, we hypothesized that lower ghrelin levels in obesity contribute to dopamine degeneration in the SNpc [16].

The animal studies described above highlight the promise for ghrelin therapy in human Parkinson's disease patients. In Parkinson's disease, patients show delayed gastric emptying and other gastrointestinal symptoms [70, 71], which may be related to disturbed ghrelin secretion in Parkinson's disease, as ghrelin affects gastroprotection and gut motility [72-75].

In order to determine ghrelin levels in Parkinson's disease patients, Unger et al. measured postprandial ghrelin in 20 healthy controls and 39 Parkinson's disease patients. Their results show that Parkinson's disease patients had significantly reduced postprandial acyl ghrelin levels relative to controls [76]. An additional study also showed that Parkinson's disease patients exhibit a paradoxical relationship between BMI and ghrelin concentrations. In normal people, high plasma ghrelin correlates with low BMI, however Parkinson's disease patients show that the lower the BMI, the lower the plasma ghrelin concentration [77]. These two studies clearly demonstrate that Parkinson's disease patients have impaired ghrelin secretion and highlight a potential therapeutic application for ghrelin in Parkinson's disease. Indeed, ghrelin is a unique hormone with potentially diverse therapeutic applications in Parkinson's disease. First, ghrelin could improve gastrointestinal dysfunction in Parkinson's disease. Second, ghrelin could prevent further nigral degeneration by acting directly on dopamine cells in the SNpc. Third, because weight loss is a common symptom of Parkinson's disease, exogenous ghrelin could help maintain normal energy homeostasis by promoting appetite and weight gain. Fourth, depression is a common symptom of Parkinson's disease and ghrelin positively affects mood and reduces anxiety [56]. Fifth, Parkinson's disease patients occasionally display learning and memory deficits and ghrelin enhances learning and memory by activating synaptic plasticity in the hippocampus [78]. These observations strongly suggest ghrelin has multiple beneficial effects on Parkinson's disease patients and no predictable side effects. Future studies should test the clinical efficacy of ghrelin treatment in Parkinson's disease patients, especially since many patients experience uncontrolled weight loss and impaired appetite regulation. This highlights the therapeutic potential of ghrelin in Parkinson's disease patients to maintain appetite and energy balance, and prevent further degeneration.

3. Glucagon like peptide 1 (GLP1)

GLP1 is a hormone produced by the proglucagon gene expressed in L cells predominantly in the lower gut (distal intestine and colon) but it is also found at lower levels in the pancreas and brain. Other proglucagon products include glucagon, glicentin, glucagon like peptide 2 and oxyntomodulin. GLP1 is a well-known satiety signal that is released into the bloodstream in response to ingested nutrients, such as fats and sugars. GLP1 inhibits food intake in several species including humans and is also a promising target to restrict diabetes since it accentuates glucose-dependent insulin release, inhibits glucagon and increases pancreatic β -cell growth [79]. GLP1 acts on the GLP1R, which is expressed in the gut, pancreas, brainstem, hypothalamus, thalamus, hippocampus and vagal afferent nerves [80-82]. The presence of the GLP1R in the brain indicates that GLP1 could have effects on neuronal function. Indeed, activation of the GLP1R promotes cell survival and plasticity including enhanced learning, protection from apoptotic cell death and from oxidative insults [83-89]. In contrast, treatment with GLP1R antagonists or studies with GLP1R knockout mice all demonstrate impaired synaptic plasticity as well as impaired learning, cognition and memory [85, 87]. These observations directly suggest that GLP1 has neuroprotective effects. For example, both central and peripheral GLP1 enhances synaptic plasticity in mice [87] and the GLP1 agonist exendin-4 increases neurogenesis in the hypothalamus [90] and stimulates both neurons and glia from neural progenitor cells in vitro and in vivo [91]. Moreover exendin-4 activates human neuronal cell differentiation and proliferation [92, 93] in vitro. Clearly, the ability to increase neurogenesis implicates GLP1 as

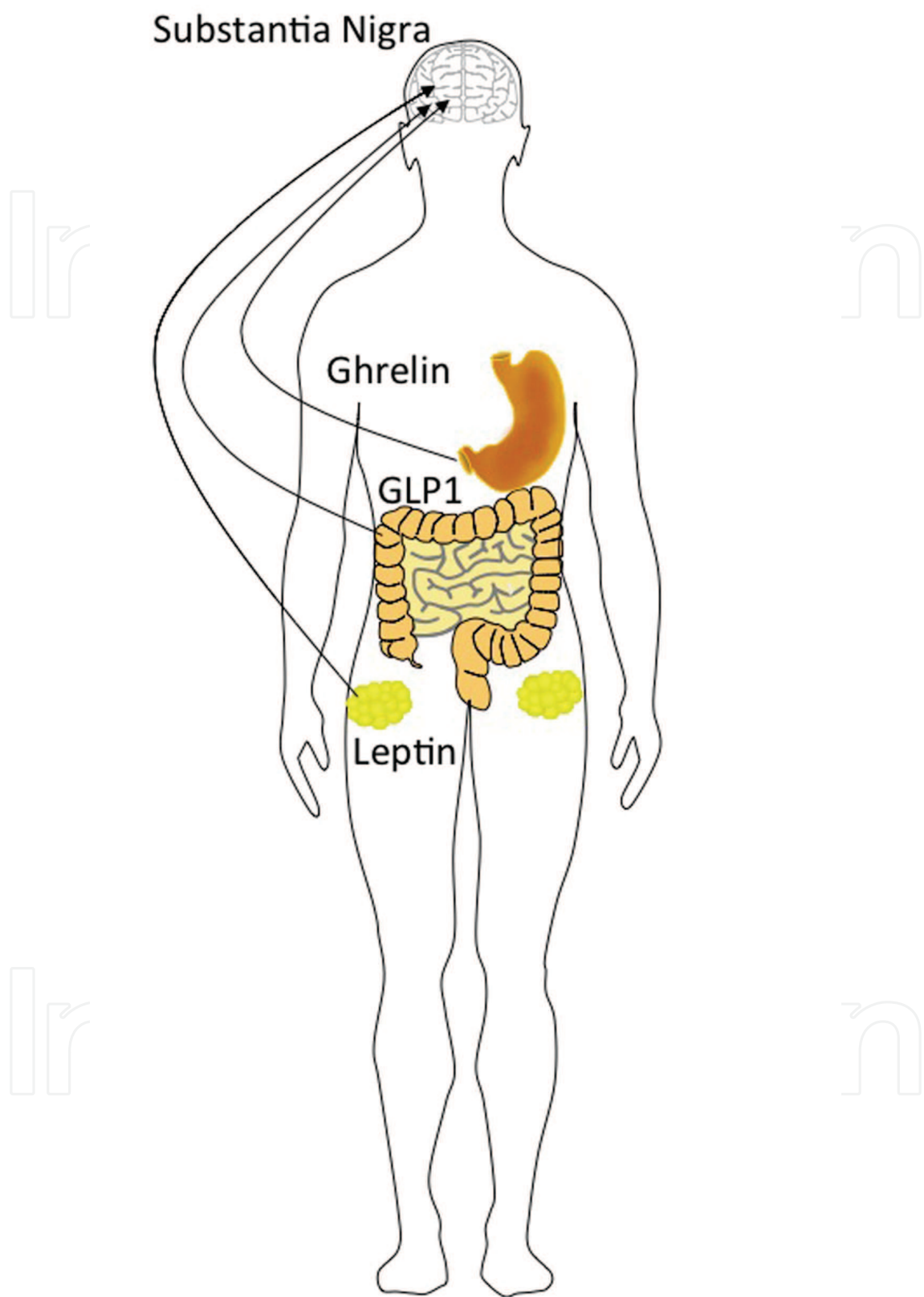


Fig. 1. Metabolic hormones directly target dopamine neurons in the substantia nigra. Ghrelin, glucagon-like peptide 1 (GLP1) and leptin receptors are all present in the substantia nigra suggesting a direct action of these hormones on dopamine neuronal function

a potential therapeutic agent that combats degeneration and facilitates regeneration in neurological disorders such as Parkinson's disease.

Recent animal studies show that GLP1 is an excellent therapeutic target to treat Parkinson's disease. For example, exendin-4 treatment for 2 weeks reduces amphetamine-induced circling behavior in 6-OHDA lesioned rats and reduced TH cell death in the SNpc [91]. The GLP1-induced neuroprotection was ascribed to neurogenesis in the subventricular zone and an increase in neural stem cells in the medial striatum. Harkavyi et al, also found similar results using two different Parkinson's disease models [94]. Exendin-4 reduced circling behavior in both 6-OHDA and lipopolysaccharide (LPS) models of Parkinson's disease. Consistent with these behavioural experiments, exendin-4 attenuated striatal dopamine loss and TH cell loss in the SNpc [94]. This study underscores the therapeutic potential of GLP1, as it showed that exendin arrests degeneration even after established nigral lesions. Li et al, detected GLP1R mRNA in both primary cortical neurons and ventral mesencephalic dopamine neurons [95]. Both GLP1 and exendin-4 prevent hypoxia and 6-OHDA-induced cell death in cells from GLP1R wild type but not GLP1R knockout mice. *In vivo*, exendin-4 protected dopamine neurons against degeneration, preserved dopamine levels and improved motor function in the MPTP mouse model of Parkinson's disease [95]. In order to characterize the neuroprotective properties of GLP1, Li et al overexpressed GLP1R in human neuroblastoma SH-SY5Y cells. Both Exendin-4 and GLP stimulated cell proliferation and cell viability by 2-fold after 24 hours and prevented hypoxia and 6-OHDA-induced cell death [93]. Exendin-4 and GLP1 ameliorated caspase 3 activity, decreased pro-apoptotic Bax and increase anti-apoptotic Bcl-2 proteins. Protein kinase A and PI3K pathways mediated the neuroprotective functions of GLP1R signaling although MAPK also played a minor role [93].

Exendin-4 has strong anti-inflammatory properties and GLP1 inhibits LPS-induced cytokine release [96, 97] and the anti-inflammatory effect of GLP1 could be mediated by promoting adipokines that target the brain to reduce neuroinflammation and improve neuroprotection [98] or by a direct effect as glia (and neurons) express the GLP1R [96]. Indeed, Kim et al, illustrated that systemic exendin-4 injection restricted the loss of dopamine neurons in the SNpc and dopamine fibers in the striatum by deactivating microglia in these regions [99]. Microglia are well described to exacerbate degeneration [21] by increasing pro-inflammatory cytokines, thus reduced microglial activation by exendin-4 in the nigrostriatal pathway suppresses degeneration. These studies highlighted above demonstrate the utility of activating GLP1R to treat Parkinson's disease. Indeed, research shows that activating GLP1R restricts degeneration not only in Parkinson's disease but also in models of Alzheimer's disease [100] and stroke [95]. The GLP1R agonist, exendin-4, provides the most attractive therapeutic potential as it has a much longer half-life than GLP1 itself (hours vs. minutes). Given that GLP1R activation with exendin-4 in animal studies provides significant neuroprotection in different models of Parkinson's disease, future studies are required to translate these findings into a clinical application. The ability of GLP1R activation to increase neurogenesis may provide long lasting protection against ongoing degeneration in Parkinson's disease patients. However, GLP1 suppresses food intake and this is an unwanted side effect in Parkinson's disease patients. Future studies need to address and circumvent these issues.

4. Leptin

Although leptin is predominantly secreted from adipose tissue and is not a gut hormone, it is pertinent to add a section on leptin and Parkinson's disease, as leptin is also an important

Figure 2

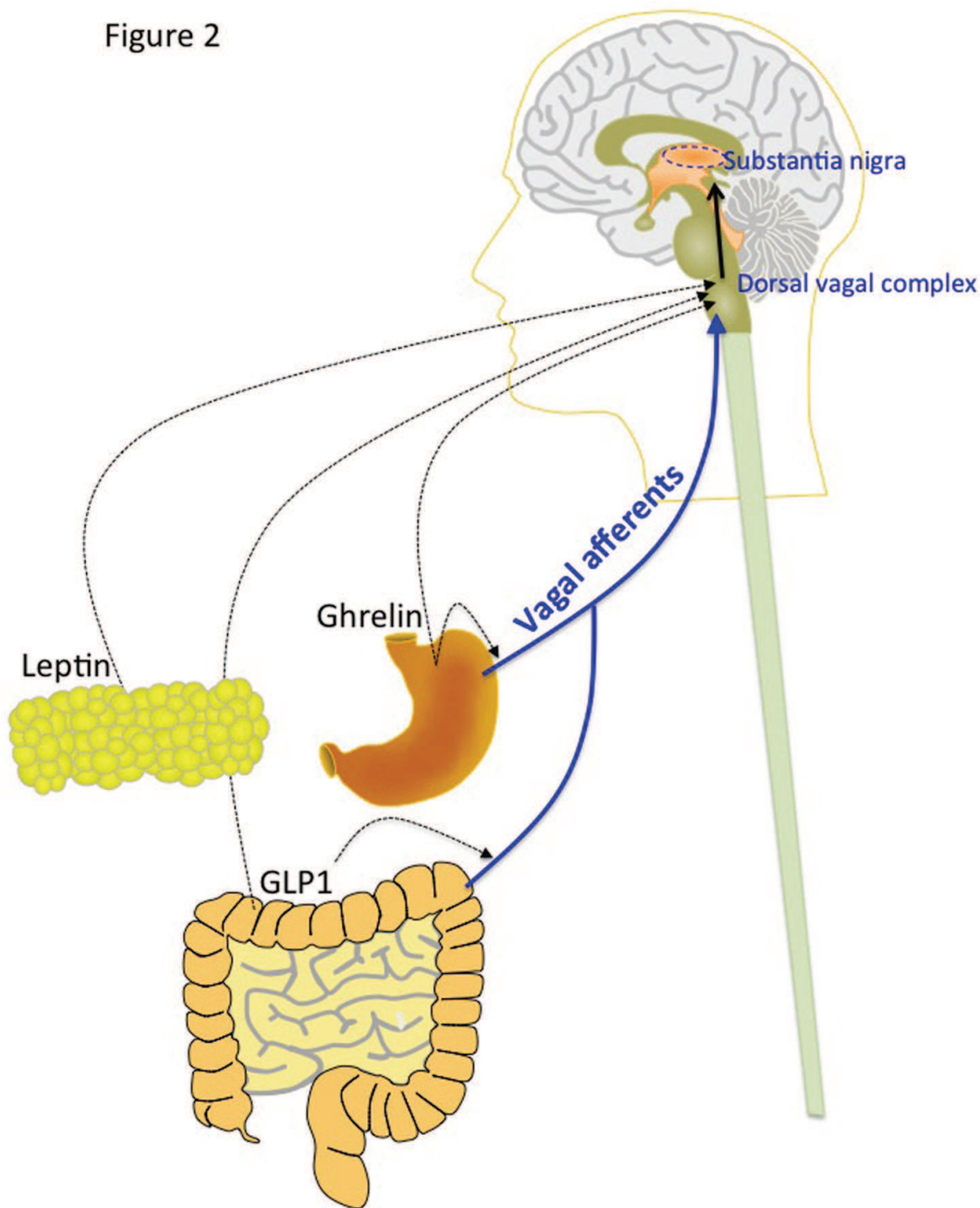


Fig. 2. Metabolic hormones indirectly target substantia nigra neurons through the brainstem. Ghrelin, glucagon-like peptide 1 and leptin receptors are present in the dorsal vagal complex. Vagal afferents from the stomach and intestines are also present in the dorsal vagal complex. Braak’s hypothesis states that dopamine dysfunction is a product of retrograde degeneration from the gut (stomach/intestines), through the brainstem (dorsal vagal complex). Ghrelin and GLP1 may promote healthy gut function and thereby restrict retrograde degeneration. This circuit highlights the complicated and integrated manner in which metabolic hormones directly and indirectly regulate higher brain function

metabolic hormone. Leptin is best known for the hypothalamic regulation of energy homeostasis, including suppressing appetite and increasing energy expenditure [101]. However, significant leptin receptor expression exists outside the hypothalamus including in midbrain dopamine neurons [102] relevant to Parkinson's disease. The first indication that leptin plays a neuroprotective role came from *in vitro* studies. Lu et al showed that leptin prevents MPP⁺-induced cell death in SH-SY5Y cells through the phosphatidylinositol 3 kinase (PI3K) pathway but not the STAT3 or MAPK pathway [103]. Leptin also protects the nigrostriatal dopaminergic system from 6-hydroxydopamine (6-OHDA) induced degeneration *in vivo* [104]. 6-OHDA treatment caused a significant loss of dopamine neurons in the SNpc and dopamine concentration in the striatum that was reversed with leptin pretreatment. The 6-OHDA model offers an additional advantage over the MPTP mouse model as it allows a quantifiable measure of motor dysfunction. These studies showed that leptin decreased apomorphine-induced asymmetrical rotations contralateral to the side of 6-OHDA injections. Leptin pretreatment attenuated key apoptotic markers such as activated caspase 9 and activated caspase 3, DNA fragmentation and cytochrome C release. ERK1/2 phosphorylation mediated the anti-apoptotic effects of leptin by recruiting pCREB in cultured dopamine neurons. pCREB is an important transcription factor in dopamine neurons that induces neuroprotection by increasing BDNF expression and leptin increased BDNF in this study.

There are conflicting reports about plasma leptin concentrations in Parkinson's disease patients. Fiszer et al reported patients with weight loss had reduced plasma leptin concentrations [77] whereas Aziz et al observed no difference in the total levels of leptin or diurnal variation [105]. These results indicate that unintended weight loss in Parkinson's disease patients is unlikely to be due to abnormal serum leptin concentrations. Current human studies have only measured plasma leptin in relation to weight loss, future studies should also examine the effect on disease progression, as animal studies highlighted above suggest that leptin may have neuroprotective effects on SNpc dopamine neurons.

5. Conclusion

Gastrointestinal dysfunction, such as constipation, is a common symptom of Parkinson's disease that is observed well before any motor dysfunction caused by dopaminergic degeneration in the nigrostriatal pathway. Recent evidence suggests that Parkinson's disease may even start in the gastrointestinal tract. According to the 'Braak's' hypothesis, protein aggregation in enteric neurons spreads in a retrograde manner to the brain through the dorsal motor nucleus of the vagus and triggers Parkinson's disease [1]. In support of this theory, mutant α -synuclein in gut enteric neurons caused gastrointestinal (GI) dysfunction followed by motor abnormalities [2] and rotenone treatment, a compound found in pesticides that causes Parkinson's-like conditions, caused enteric neuronal α -synuclein accumulation and GI dysfunction in rats before neuronal protein aggregation [3, 4]. These studies, taken together with the early GI disturbances in humans, clearly implicate the GI system in the pathogenesis of Parkinson's disease. This chapter highlights recent work on two important gut hormones, ghrelin and GLP1, that also regulate nigrostriatal dopamine function. It is interesting to note that both hormones influence gut function, neuronal metabolism, appetite and peripheral energy metabolism, suggesting a novel link between neurodegeneration and energy metabolism. Future studies are required to translate promising results in animal studies into clinical therapies.

6. Acknowledgements

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7. References

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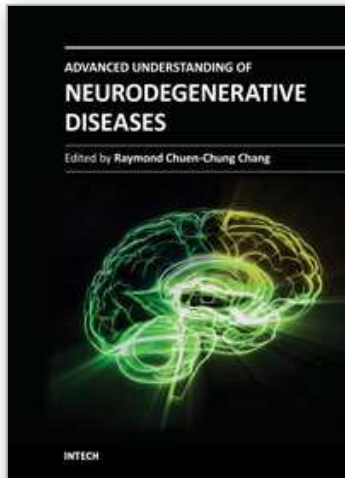
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Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis and spinal muscular atrophy. This book provides a clear explanation of different neurodegenerative diseases with new concepts of understand the etiology, pathological mechanisms, drug screening methodology and new therapeutic interventions. Other chapters discuss how hormones and health food supplements affect disease progression of neurodegenerative diseases. From a more technical point of view, some chapters deal with the aggregation of prion proteins in prion diseases. An additional chapter to discuss application of stem cells. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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