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REVIEW

Neuroprotective Effects of Brain-Gut Peptides: A Potential Therapy for Parkinson's Disease

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Abstract Parkinson's disease (PD) is the second most common neurodegenerative disease and is typically associated with progressive motor and non-motor dysfunctions. Currently, dopamine replacement therapy is mainly used to relieve the motor symptoms, while its long-term application can lead to various complications and does not cure the disease. Numerous studies have demonstrated that many brain-gut peptides have neuroprotective effects in vivo and in vitro, and may be a promising treatment for PD. In recent years, some progress has been made in studies on the neuroprotective effects of some newly-discovered brain-gut peptides, such as glucagon-like peptide 1, pituitary adenylate cyclase activating polypeptide, nesfatin-1, and ghrelin. However, there is still no systematic review on the neuroprotective effects common to these peptides. Thus, here we review the neuroprotective effects and the associated mechanisms of these four peptides, as well as other brain-gut peptides related to PD, in the hope of providing new ideas for the treatment of PD and related clinical research.

Keywords Parkinson's disease · Glucagon-like peptide 1 · Pituitary adenylate cyclase activating polypeptide · Nesfatin-1 · Ghrelin

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Introduction

Parkinson's disease (PD) is a progressive age-related degenerative disease with the loss of dopaminergic neurons (DA neurons) in the substantia nigra, leading to progressive motor impairment including akinesia, bradykinesia, hypokinesia, postural instability, rigidity, stooped posture, and tremor at rest, which commonly present along with gait impairment [1]. Furthermore, various non-motor symptoms are also involved including hyposmia, constipation, depression, appetite and rapid eye movement sleep behavior disorder [2, 3]. DA replacement therapy is widely used to improve the motor impairment, while long-term application can lead to various complications and cannot cure the disease.

It is widely accepted that PD is often associated with a variety of gastrointestinal symptoms [4], suggesting that dysfunction of the brain-gut axis might be involved in its occurrence. For this reason, a link between brain-gut peptides and the central nervous system (CNS) has been considered. Numerous studies have demonstrated that many brain-gut peptides have neuroprotective effects in vivo and in vitro, improving the motor impairment in PD. The mechanisms of their neuroprotective effects may be related to anti-inflammation, anti-oxidative stress, anti-apoptosis, neurotrophic action, and autophagy.

In this review, we discuss the common neuroprotective effects on PD and associated molecular mechanisms of brain-gut peptides including glucagon-like peptide 1 (GLP-1), pituitary adenylate cyclase activating polypeptide (PACAP), nesfatin-1, and ghrelin, as well as their latest application in the treatment of PD. In addition, the prospect of the potential treatment of PD by some brain-gut peptides is also presented.

GLP-1

GLP-1, a 30-amino-acid peptide hormone, is the transcription product of a pro-glucagon gene. Nutrients absorbed in the small intestine induce GLP-1 secretion from L cells in the ileum [5]. Distributed in central and peripheral regions, it can freely cross the blood-brain barrier (BBB) by diffusion, so most of the GLP-1 in the CNS is from the periphery, while it is also produced by neurons and glial cells [6]. The GLP-1 receptor (GLP-1R), a G-protein-coupled receptor, is widely expressed not only in the pancreas, but in most regions of the brain as well as other organs, such as in the kidney, heart, lung, intestine, and stomach [7]. GLP-1 has a variety of biological functions, including inhibition of gastric emptying and intestinal peristalsis, stimulation of insulin secretion, inhibition of glucagon secretion, reduction of appetite and food intake, weight reduction, and protection against β cell apoptosis [8]. In addition to the effects on the digestive system, it has been suggested that GLP-1 has protective effects on the cardiovascular system and takes part in the regulation of bone turnover. Moreover, neuroprotective effects of GLP-1 have also been demonstrated [9].

Although currently there are no large-scale statistical data to show that PD is directly related to changes in the GLP-1 levels, a substantial number of epidemiological studies indicate that there is a higher risk for several neurodegenerative diseases including PD among people with type 2 diabetes mellitus (T2DM) [10, 11]. And dysregulated insulin signaling due to the development of insulin resistance may underlie the pathological processes shared by T2DM and PD and furthermore can influence neurodegeneration [6].

In the past few years, many drugs related to GLP-1 have been approved by the Food and Drug Administration for the treatment of diabetes [12], such as the GLP-1R agonists liraglutide, exenatide, and exenatide extended-release, which have a long half-life and stability, and inhibitors of dipeptidyl peptidase 4 (DDP-IV), an exopeptidase that inactivates GLP-1, such as sitagliptin, saxagliptin, linagliptin, and alogliptin. Most of these have been used as experimental agents to explore the neuroprotective effects of GLP-1 on PD. Besides, some are the subject of ongoing clinical trials in PD, such as exenatide and liraglutide.

Many studies have indicated that GLP-1 analogues have neuroprotective effects and improve the motor impairment in PD models [13, 14]. In a study using the PD rat model induced by rotenone, the levels of tumor necrosis factor alpha (TNF-α) and malondialdehyde (MDA), an indicator of oxidative stress, decreased distinctly after exenatide treatment. Besides, exenatide-treated rats had lower apomorphine-induced rotation test scores, and it significantly reduced the loss of DA neurons in the striatum of the treated group compared with the control group [13]. Another study based on PD rodent models suggested that, in the group treated with sitagliptin and liraglutide, the pro-apoptotic protein Bax and the pro-inflammatory cytokines including interleukin (IL)-1β, IL-6, and transforming growth factor-β1 decreased, while the anti-apoptotic protein Bcl-2 and the levels of striatal DA, nigral glial cell line-derived neurotrophic factor (GDNF), and tyrosine hydroxylase-positive cells clearly increased [14]. These studies suggest that GLP-1 has anti-inflammatory, anti-apoptotic, and antioxidant effects in PD models [13, 14]. In addition, it has been demonstrated that GLP-1 analogues and DDP-IV inhibitors have neurotropic effects, which promote neuron growth and the processes of synaptic plasticity in PD models [7, 14–16].

Abnormal activation of microglia plays a role in neuroinflammation and oxidative stress in PD. GLP-1 reduces oxidative stress and apoptosis in microglia, affecting several of their important homeostatic functions. It has been demonstrated that in BV-2 microglia, GLP-1 inhibits the accumulation of intracellular reactive oxygen species (ROS) and release of nitric oxide, as well as increasing the expression of the antioxidants glutathione peroxidase 1 (GPx1) and superoxide dismutase 1 (SOD1), which reduce oxidative stress. And GLP-1 reduces the apoptosis of microglia by inhibiting caspase-3/7 activity and lowering the level of TNF-α. Moreover, GLP-1 also upregulates the expression of the brain-derived neurotrophic factor (BDNF), GDNF, and nerve growth factor by BV-2 microglia [17]. And the anti-inflammatory effects of GLP-1 are now considered to be mediated by multiple signaling pathways. In primary mouse microglia, the activation of GLP-1 activates phosphoinositide 3-kinase (PI3K), which triggers downstream protein kinase B (AKT), and through the PI3K/AKT pathway, the activation of GLP-1Rs leads to the inhibition of nuclear factor-kappa B (NFκB), a key factor in the occurrence of inflammation, which inhibits the activation of microglia and release of pro-inflammatory factors [7, 18, 19]. Moreover, another study of primary rat cortical astrocytes indicated that the anti-inflammatory effect of liraglutide is also mediated by the cyclic AMP (cAMP)/protein kinase A (PKA)/cAMP response element-binding protein (CREB) signaling pathway, which inhibits pro-inflammatory factors including TNF-α, IL-6, and IL -1β [20].

Mitochondria are the major producers of ROS, as well as being susceptible targets of ROS and oxidative stress. It has been demonstrated that GLP-1 preserves the function of mitochondria mainly by elevating the mitochondrial membrane potential, promoting mitochondrial biogenesis, and improving the activity of mitochondrial antioxidant

enzymes such as Mn-SOD, catalase, and glutathione peroxidase, and its effects may be cooperative with the inhibition of glycogen synthase kinase 3 beta (GSK-3β) [19, 21]. The molecular mechanism of the anti-oxidant effect of GLP-1 is now considered to be mainly accomplished by the PI3K/AKT/GSK-3β pathway. After PI3K activation, GSK-3β is inhibited through the AKT pathway, which reduces oxidant stress [22]. Besides, another study indicated that a GLP-1R agonist protects PC12 cells against oxidative damage via the c-Raf/mitogen-activated protein kinase kinase (MEK)/mitogen-activated protein kinase (MAPK) pathway, which enhances the expression of anti-oxidative proteins including heme oxygenase-1 and Bcl-2 (B cell lymphoma 2) [23] Moreover, in a study based on rat β cells, GLP-1 effectively improved their antioxidant capacity via PKA-dependent activation of extracellular regulated protein kinases (ERK) and nuclear factor erythroid 2-related factor 2 (Nrf2) nuclear translocation, a factor that regulated cellular stress responses, induces the expression of antioxidant and detoxification enzymes, and protects against oxidative stress-induced cell damage [24]. However, further research is still needed to determine whether this pathway plays a role in neurons or glial cells. And another study [25] suggested that acting on the receptor for advanced glycation end product (RAGE), vildagliptin, a DDP-IV inhibitor, exerted its anti-oxidant effects in rat rotenone PD models via the RAGE/Nrf2 signaling pathway, which reduces the neutrophil infiltration marker myeloperoxidase and oxidative stress in the striatum.

It has been demonstrated that GLP-1 and it analogues have anti-apoptotic effects on DA neurons. For example, in PD mouse models induced by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), geniposide, a novel GLP-1 agonist, upregulates the expression of Bcl-2 with subsequently reduced caspase 3 activation, resulting in the preservation of DA neurons [19]. The detailed signaling pathway has been indicated by another study based on cortical neurons. This study showed that GLP-1 increases the expression of phosphorylated AKT and ERK but decreases the expression of phosphorylated p38 and c-jun-NH2-terminal kinase in vitro, which has also been reported in the right cerebral cortex of rat models of middle cerebral artery occlusion. Besides, the anti-apoptotic effects are reduced by inhibitors of PI3K and/or ERK, which suggests that the effects are achieved by the PI3K/AKT and ERK pathways. And the Bcl-2/Bax ratio is increased via these pathways, while the caspase 3 system is inhibited, exerting the anti-apoptotic effects of GLP-1 [26].

Furthermore, GLP-1 has neurotrophic effects and promotes neurogenesis. A study based on human neuroblastoma SH-SY5Y cells suggested that GLP-1 stimulates cell proliferation and increases cell viability, and this trophic action is primarily mediated through the PKA and PI3K pathways since the selective inhibition of either PKA or PI3K signaling abolishes these effects. These pathways can activate CREB, which could increase the level of BDNF. By contrast, this study suggested that MEK1/2 signaling have a minor or no effect on GLP-1-mediated neuronal proliferation [27]. However, another in vitro study suggested that GLP-1 promotes cortical neurite outgrowth, and the effect was partially suppressed by an MAPK–ERK inhibitor, suggesting that the effect was at least partially achieved by the MEK–ERK/CERB pathway [28]. Thus, the signaling pathway involved in the neurotrophic effects of GLP-1 is not very clear.

GLP-1 analogues have also been shown to have neuroprotective effects on PD in clinical studies. A small, proof-of-concept, open-label trial in which PD patients were treated with exenatide, a GLP-1 analogue, has shown that the motor and non-motor symptoms of the treated group improved more than the control group [29]. Furthermore, the improvement still existed beyond the 12-month period of exenatide exposure [30]. Next, a single-center, double-blind, randomized, placebo-controlled trial, in which moderate PD patients were treated with exenatide or placebo once a week for 48 weeks, followed by a washout period of 12 weeks was carried out [31]. The results strongly suggested that GLP-1 analogues has positive effects on the symptoms of PD, though commonly with slight weight loss.

In addition, some studies based on PD rat models indicated that novel dual GLP/GIP (glucose-dependent insulinotropic polypeptide) receptor agonists with few side effects, such as DA-CH3 and DA-JC4, have neuroprotective effects superior to a single GLP-1 R agonist [32]. Furthermore, a triple receptor agonist is currently under development. In brief, GLP-1 analogues may be a promising therapy for PD, while further research is still needed before they go on the market.

PACAP

PACAP, a neuropeptide composed of 32 amino-acids that belongs to the vasoactive intestinal polypeptide (VIP)-secretin-growth hormone-releasing hormone-glucagon superfamily, is widely distributed in tissues, especially in the gastrointestinal system and brain [33]. PACAP has two isoforms, PACAP38 and PACAP27. PACAP38 is actively transported across the BBB, while PACAP27 crosses the BBB by diffusion across the membrane [34]. It works through three major receptors: the PAC1 receptor (PAC1R), the VPAC1 receptor (VPAC1R), and the VPAC2 receptor (VPAC2R) [33].

In the digestive system, PACAP regulates gastrointestinal tract motility [35], and stimulates the secretion of

saliva, gastric acid, and bicarbonate as well the release of other regulatory peptides including gastrin, somatostatin, atrial natriuretic factor, and peptide YY. Besides, PACAP stimulates insulin and glucagon secretion. And due to the wide distribution in the body, PACAP has complex biological functions in many other systems, such as stimulation of thyroxine secretion, regulation of reproductive function, bronchodilation, immune modulation, stimulation of cell proliferation and/or differentiation, stimulation of steroid hormone secretion from adrenocortical cells, promotion of adrenal gland development, and anti-apoptosis in cardiomyocytes [33].

The link between changes in PACAP levels in the brain and PD need further research, and related studies at present are very limited. Interestingly, it has been demonstrated that the DA neurons in the substantia nigra of PACAP-knockout mice are more vulnerable to paraquat (a pesticide that increases the risk of PD) than the wild type [36]. Furthermore, data support the idea that PACAP improves the motor symptoms of PD [36–38], and has neuroprotective effects against commonly-used neurotoxic agents such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), 6-OHDA (6-hydroxydopamine), and glutamate [39].

A recent study in a cellular model of PD has demonstrated that PACAP38 and its analogues have neuroprotective characteristics superior to PACAP27 [40]. The anti-apoptotic effects are mainly mediated by the PAC1R, while the VPAC1R contributes to the anti-inflammatory effects. Besides, other side effects, such as dilating blood vessels, are mainly mediated by the VPAC2R [41]. For the above reasons, selective receptor agonists have been developed. It has been demonstrated that the selective receptor agonist Ac-[Phe(pI)^{6},Nle^{17}]PACAP(1–27), an anti-inflammatory and anti-apoptotic peptide, have fewer cardiovascular side-effects and better stability in PD models in vivo and in vitro than the native peptide hormone [41].

The anti-apoptotic effect is one of the important mechanisms underlying the neuroprotective effect of PACAP. In a study based on neuronally-differentiated PC12 cells treated with rotenone, activation of the PAC1R increases the activity of adenylate cyclase (AC), making cAMP accumulate. Downstream of PKA, ERK is activated through Rap1 and Ras, which inhibit the expression of the cJun gene closely associated with apoptosis. Besides, activated ERK regulates c-fos gene expression and thus increases Bcl-2, both of which decrease the level of Bax. Via this signaling pathway, PACAP prevents the release of cytochrome c and inhibits caspase-9, which in turn regulates caspase-3, the key factor in apoptosis [33, 42, 43]. Moreover, a study based on primary cultures of cerebellar granule cells has suggested that, in addition to the cAMP/PKA signaling pathway, PACAP also activates the PI3K/AKT pathway, which also inhibits caspase-3 and exerts an anti-apoptotic effect [44].

The high levels of unsaturated lipids and high metabolic rate contribute to the fact that the CNS is more vulnerable to oxidative stress. It is widely known that astrocytes play an important role in anti-oxidative stress via many mechanisms including catalase antioxidant enzymes and SOD [45]. However, astrocytes themselves are also susceptible to oxidative stress. Numerous studies have demonstrated that, in combating oxidative stress, PACAP has neuroprotective effects on many types of cells such as neurons and astrocytes. In astrocytes, PACAP mainly exerts its neuroprotective effects through the AC/PKA, phospholipase C (PLC)/diacylglycerol (DAG)/protein kinase C (PKC), and MAPK/ERK pathways [46]. Via these signaling pathways, PACAP prevents the inhibition of SOD and catalase activity, the increase in caspase-3 mRNA levels, mitochondrial respiratory chain damage, and the accumulation of superoxide anion [47]. Otherwise, mitochondrial dysfunctions are closely associated with apoptosis caused by oxidative stress. Impaired mitochondrial integrity, increased respiratory rate, and ROS-induced mitochondrial dysfunction are all reduced by treatment with PACAP [47, 48]. To summarize, PACAP mainly exerts its neuroprotective effects against oxidative stress by inhibiting the ROS and the activation of caspase3 through the PKA, PKC, and MAPK signaling pathways.

Neuroinflammation triggered by the activation of glial cells drives the progression of neurodegenerative diseases, including PD [49]. Numerous studies have demonstrated that PACAP has anti-inflammatory effects not only in the CNS [36, 50], but in the periphery, such as the airway [51], intestine [52] and kidney [53]. In a study based on SH-SY5Y DA cells, it has been demonstrated that PACAP pretreatment protects against inflammation-mediated toxicity, and PACAP reverses the decreases in BDNF and phosphorylated CREB (p-CREB) induced by inflammatory mediators. This suggests that phosphorylation of CREB by PACAP results in BDNF induction, which leads to reduced caspase-3 levels and/or activity, and therefore inhibition of neuronal apoptosis and toxicity [54]. Besides, PACAP has its effects by maintaining the balance between pro- and anti-inflammatory cytokines. When inflammation occurs, the PACAP level is up-regulated in neurons and immune cells, which inhibits the production of pro-inflammatory cytokines such as TNF-α, interferon-γ, and IL-6 in vitro and in vivo, and stimulates the release of anti-inflammatory cytokines including IL-10 and IL-1 [50]. PACAP down-regulates the expression of pro-inflammatory cytokines mainly through the classical PKA signaling pathway, resulting in the attenuation of NFκB [50]. Besides, PACAP down-regulates Toll-like receptor 4 (TLR4), myeloid

differentiation protein 88 (MyD88), and NFκB, suppressing the activation of the TLR4/MyD88/NFκB signaling pathway, and decreasing the inflammatory cytokine levels and apoptosis in microglia [55].

The neurotrophic effect of PACAP has also been demonstrated in numerous studies. A study based on SH-SY5Y DA cells demonstrated that Salsolinol, an endogenous DA metabolite selectively toxic to DA neurons, decreases the BDNF level and its signal transduction protein, p-CREB, both of which are attenuated by PACAP treatment; in addition, PACAP promotes DA synthesis [56]. In neurons, several signaling pathways account for the upregulation of BDNF, one of which is a Ca^{2+}-dependent pathway. PACAP directly activates the AC/PKA or the PLC/PKC pathway, both of which activate the N-methyl-D-aspartate receptor/Ca^{2+}/calcineurin/CREB-regulated transcriptional coactivator 1/CREB signaling pathway, causing the expression of BDNF mRNA. The other is the Ca^{2+}-independent pathway, in which PACAP phosphorylates CREB directly through the AC/PKA and PLC/PKC pathways via the PAC1R [57].

In brief, PACAP has neuroprotective effects in PD models, while its complex pharmacological actions, as well as the short half-life, limit its clinical application. Further research is needed to determine whether PACAP can become a promising pharmacological target for the treatment of PD.

Nesfatin-1

Nesfatin-1, an 82-amino-acid anorexigenic polypeptide proteolytically cleaved from Nucleobindin 2, was discovered in 2006 [58], and it has a wide distribution both in the CNS and peripheral regions [59]. Besides, nesfatin-1 can penetrate the BBB in both the blood-to-brain and brain-to-blood directions via non-saturable mechanisms [60]. Numerous studies [61, 62] have demonstrated that nesfatin-1 interacts with a G protein-coupled receptor to exert it biological effects, while the corresponding receptor has not yet been cloned.

In addition to the originally-discovered effects in the digestive system (loss of appetite, inhibition of gastric emptying and gastric acid secretion, and regulation of gastroduodenal motility), nesfatin-1 has other important functions, many of which are related to energy homeostasis, such as energy expenditure and glucose homeostasis. Besides, it also plays a role in increasing blood pressure and heart rate, the stress response, behavior, sleep, and reproduction [63].

Interestingly, a study showed that nesfatin-1 postsynaptically suppresses the electrical activity of nigral DA neurons [64]. Besides, it has been suggested that the abnormal electrophysiological properties of DA neurons might be responsible for their vulnerability in PD [65]. In order to identify the effect of nesfatin-1 on PD, another experiment [66] finally demonstrated that nesfatin-1 has similar protective effects on DA neurons both in vivo and in vitro, suggesting that it might have therapeutic potential for PD. The neuroprotective effect of nesfatin-1 may be associated with anti-apoptosis, anti-inflammation, and anti-oxidant stress. However, there is not enough evidence at present to support a link between PD and changes of nesfatin-1 levels.

The anti-inflammatory effect of nesfatin-1 in brain has been demonstrated in numerous studies. A study [67] based on rat models of traumatic brain injury showed that the administration of nesfatin-1 significantly decreases the gene expression of NFκB and the concentrations of TNF-α, IL-6, and IL-1β, suggesting that nesfatin-1 might suppress NFκB-dependent inflammatory responses. Besides, another study demonstrated that acute brain injury after subarachnoid hemorrhage-induced neutrophil infiltration and the increasing levels of pro-inflammatory cytokines are also inhibited by nesfatin-1 treatment [68].

The antioxidant capacity of nesfatin-1 has been proposed as a possible mechanism for its neuroprotective potential. It is widely accepted that the antioxidant system is responsible for the balance between the formation and elimination of ROS. And ROS in mitochondria increase the mitochondrial membrane permeability, which causes the leakage of cytochrome C into the cytoplasm, inducing caspase-3-dependent apoptosis [69]. Interestingly, nesfatin-1 in MES23.5 DA neurons has been shown to rescue the mitochondrial transmembrane potential collapse induced by rotenone and restore the function of mitochondrial respiratory chain complex I [70]. Besides, a recent study also strongly suggested that nesfatin-1 inhibits lipid peroxidation and increases the activity of antioxidant enzymes (SOD and GSH) in cerebral ischemia [71]. Moreover, the antioxidant capacity of nesfatin-1 has also been demonstrated in models of subarachnoid hemorrhage [68].

Pretreatment with nesfatin-1 protects MES23.5 DA neurons against rotenone-induced neurotoxicity by its anti-apoptotic effect and ameliorating mitochondrial dysfunction [70]. Further study [66] by this team showed that the anti-apoptotic effect of nesfatin-1 in DA neurons is achieved through the C-Raf/ERK1/2-dependent anti-apoptotic pathway, through which nesfatin-1 markedly suppresses the activity of caspase-3, leading to the inhibition of apoptosis. Moreover, in this study, the inhibitor of PKA did not block the effect of nesfatin-1, suggesting that the PKA pathway is not involved in the anti-apoptotic mechanism.

The molecular mechanisms of the neuroprotective effects of nesfatin-1 have yet to be fully identified, because

the corresponding receptor has not been cloned. A study in the NB41A3 neural cell line indicated that nesfatin-1 might utilize Ca^{2+} influx and/or the MAPK signaling pathway to phosphorylate CREB rather than the PKA pathway [62]. On the contrary, another study suggested that the activation of PKA is closely associated with Ca^{2+} influx in rat hypothalamic neurons [72]. The opposite results may be due to the differences between hypothalamic neurons and NB41A3 cells. Besides, one study indicated that PKC pathway is responsible for the Ca^{2+} influx in rat dorsal root ganglion neurons [61]. Taken together, the detailed molecular mechanisms still need to be studied.

It is worth noting that nesfatin-1 downregulates the level of GNDF, which decreases exploration and induces anxiety-like behavior in rats [73]. Besides, although the mechanisms underlying neuroprotective effects of nesfatin-1 have been demonstrated in a variety of models of neurological disease, whether these mechanisms involved in neuroprotection are applicable to PD remains to be determined. Thus, long-term research is still needed before nesfatin-1 can be used in clinical practice.

Ghrelin

Ghrelin, a 28-amino-acid peptide hormone discovered in 1999 [74], stimulates growth hormone (GH) release from the anterior pituitary as the endogenous ligand for GH secretagogue receptor (GHSR)1a, which is expressed predominantly in the anterior pituitary, pancreatic islets, adrenal gland, thyroid, myocardium, hippocampus, substantia nigra pars compacta, ventral tegmental area, and raphe nuclei [75]. Importantly, ghrelin occurs in the plasma in two major forms, acyl-ghrelin (AG) and unacylated ghrelin (UAG) [76]. The acylation of ghrelin not only contributes to the specificity of its transport across the BBB [77], but facilitates its binding to GHSR1a [74].

Ghrelin has a wide range of functions in the digestive system including regulation of food intake, glucose metabolism and adiposity, stimulation of gastric acid secretion and gut motility. Besides, it also modulates anxiety and stress, protects against muscle atrophy, improves cardiovascular functions, and modulates sleep [75].

Furthermore, accumulating evidence suggests that ghrelin, as a neuron survival agent, is closely associated with PD. And in a recent study [78], a significant decrease in GHSR expression was reported in PD-specific induced pluripotent stem cell -derived DA neurons generated from patients carrying parkin gene (PARK2) mutations compared to those from healthy controls, and delivery of a selective GHSR1a inhibitor into the substantia nigra pars compacta of normal mice induced PD-like motor dysfunction. Besides, a reduced postprandial ghrelin response in patients at clinical or presumably pre-clinical stages of PD, was observed in another study, which suggested ghrelin might qualify as a potential peripheral PD biomarker [79]. Besides, it has also been demonstrated by another recent study that total and active plasma ghrelin levels are decreased in PD patients; moreover, pre-prandial peak responses and post-prandial ghrelin suppression are both attenuated in PD [80], indicating a close link between ghrelin and PD.

A new ghrelin agonist, HM01, alleviates constipation and L-dopa-delayed gastric emptying in the mouse model of PD induced by 6-OHDA, suggesting effects on non-motor dysfunction of PD [81]. In addition, it is worth noting that ghrelin increases DA release and turnover in the striatum by inhibiting voltage-gated K^+ Kv7/KCNQ/M channels through its receptor GHS-R1a and activation of the PLC/PKC pathway [82]. And inhibition of the Kv7/KCNQ channel has been shown to have neuroprotective effects against 6-OHDA-induced degeneration of the nigrostriatal DA system and motor dysfunction, so it might be a potential target for treatment of PD [83]. Moreover, ghrelin, in various studies, has also been shown to have neuroprotective effects in PD models [84–86], and might be involved in anti-apoptotic, anti-inflammatory, anti-oxidant stress, and neurotrophic effects, as well as autophagy.

The anti-apoptotic effects of ghrelin in brain, in vivo and in vitro, have been indicated in various studies. Ghrelin antagonizes the apoptosis of nigral DA neurons induced by MPTP [87]. In this study, compared to the control group, the administration of ghrelin contributed to a clear increase in the Bcl-2 level, while the Bax level was suppressed, accompanied by the inhibition of caspase-3. Besides, a study based on primary rat cortical neurons suggested that the anti-apoptotic effects of ghrelin may also be mediated by the PI3K/AKT signaling pathway, resulting in an increase of the nuclear translocation of β-catenin and the inhibition of GSK-3β, a pre-apoptotic protein [88]. In addition, ghrelin attenuates apoptosis in hypothalamic neurons during oxygen-glucose deprivation. This study demonstrated that ghrelin contributes to marked activation of ERK1/2 and triggers downstream signals, exerting anti-apoptotic effects. And ghrelin-induced activation of ERK1/2 and the anti-apoptotic effect were eliminated by the inhibition of PKA, PKC, MAPK, and PI3K [89], suggesting that these signaling pathways are involved in its anti-apoptotic effects.

A recent study [90] demonstrated that ghrelin suppresses oxidative stress in dorsal root ganglia neurons induced by paclitaxel by restoring mitochondrial function. In this study, peroxisome proliferator-activated receptor gamma coactivator 1-alpha was induced by ghrelin, which

increased the number of mitochondria. Besides, It also increased the level of SOD2 and Uncoupling protein 2 (UCP2), a mitochondrial protein that decreases reactive ROS. And it has been demonstrated that ghrelin exerts its neuroprotective effects via a UCP2-dependent mitochondrial mechanism in models of PD [91] and traumatic brain injury [92]. Moreover, ghrelin protects MES23.5 cells against the cytotoxicity induced by 1-methyl-4-phenylpyridinium ion. In this study, ghrelin lowered the level of MDA and THE Bax/Bcl2 ratio and improved the levels of Cu–Zn SOD and catalase, all of which might be mediated by inhibition of the NFκB pathway [93].

Autophagy also plays an important role in maintaining cellular homeostasis, disorder of which has been deemed one of the pathogenic factors of neurodegenerative diseases. Besides, a correlation between autophagy and PD has been demonstrated by numerous studies [94]. Calorie restriction (CR) has dramatic neuroprotective effects on neurodegenerative diseases, and may be a promising therapy for PD [95]. It has been suggested that the beneficial effects of CR are most likely mediated by ghrelin, and CR induces autophagy in rat cortical neurons to exert its neuroprotective effects through neuropeptide Y and ghrelin receptor activation [96]. Furthermore, autophagy induced by ghrelin attenuates the liver injury induced by non-alcoholic fatty liver disease [97], and protects the small intestinal epithelium against sepsis-induced injury [98] and vascular calcification [99]. One of the related molecular mechanisms is the AMPK/mTOR (mechanistic target of rapamycin) signaling pathway. More specifically, in PD models induced by MPTP, when ghrelin binds to GHSR1a, the activated downstream AMPK inhibits the phosphorylation of mTOR, removing its inhibitory effect on autophagy [100]. Furthermore, activated AMPK increases the number of autophagosomes and phosphorylated unc-51-like kinase (ULK), an autophagy-related protein, which directly induces autophagy [94, 101]. Besides, in neuronal models of PD, the CaMK/AMPK/SIRT signaling pathway is involved in the mechanisms of the autophagy induced by ghrelin [94].

It has been demonstrated that ghrelin, as an anti-inflammatory agent, suppressing the cerebral cortical inflammation in epileptic rats induced by pilocarpine via inhibiting NFκB and TNF-α [102], Besides, ghrelin attenuates the secretion of IL-6, a pro-inflammatory factor, in mid-brain DA neurons induced by lipopolysaccharide [103]. Activated microglia and astroglia release many inflammatory factors, triggering downstream inflammatory responses. A study [86] showed that ghrelin suppresses MPTP-induced microglial activation and the release of pro-inflammatory mediators in the substantia nigra pars compacta and striatum, having neuroprotective effects. And due to the lack of GHSR1a in microglia, inhibition of the activation of microglia is achieved by indirectly suppressing matrix metalloproteinase-3 gene expression in stressed DA neurons. Furthermore, by acting on GHSR1a of astroglia, ghrelin also prevents their activation, avoiding the excessive release of pro-inflammatory factors that affect neurons and endothelial cells in neurodegenerative or injury processes [104].

It has been demonstrated that the peripheral administration of AG to mouse models significantly enhances hippocampal neurogenesis and synaptic plasticity, while the systemic administration of physiological levels of AG produces long-lasting improvements in spatial memory that persist after the end of treatment [105], and so might be a potential therapeutic target for neurodegenerative diseases such as PD and Alzheimer's disease. Furthermore, the neurogenesis effect of UAG, independent of GHSR, has also been demonstrated in another study based on primary cultured cells from the fetal spinal cord [106]. As noted above, most of the beneficial effects of CR are mediated by ghrelin: CR significantly enhances the levels of neurotrophic factors including GDNF and BDNF, attenuating the neurochemical and behavioral deficits in primate models of PD [107]. However, further research is still needed to determine whether this neurotrophic effect is mediated by ghrelin or not.

In summary, numerous pre-clinical studies have shown that ghrelin has neuroprotective effects, and may be a novel potential target for the treatment of PD and other neurodegenerative diseases. However, currently available studies cannot confirm that ghrelin has any clinical benefit in PD patients. Thus, long-term research is needed before ghrelin can be used in clinical practice (Fig. 1).

Other Brain-Gut Peptides Associated with PD

In addition to the four peptides discussed above, many brain-gut peptides have been reported to participate in PD, such as vasoactive intestinal peptide (VIP), pancreatic polypeptide (PP), and neurotensin (NT). It has been clearly demonstrated that VIP has a neuroprotective effect on DA neurons, microglia, and astrocytes, and may be a promising target for the treatment of PD [108] It is notable that PACAP belongs to the VIP/glucagon/secretin family, showing particularly high homology (68%) to VIP. Because of the high homology of the amino-acid sequences of PACAP and VIP, these peptides share the same receptors [109]. Thus, the mechanisms of the neuroprotective effects of PACAP and VIP, as well as the signaling pathways, are almost identical.

PP, a 36-amino-acid peptide, may function as an important feedback inhibitor of pancreatic secretion after a meal. It arises from both islet and acinar cells of the

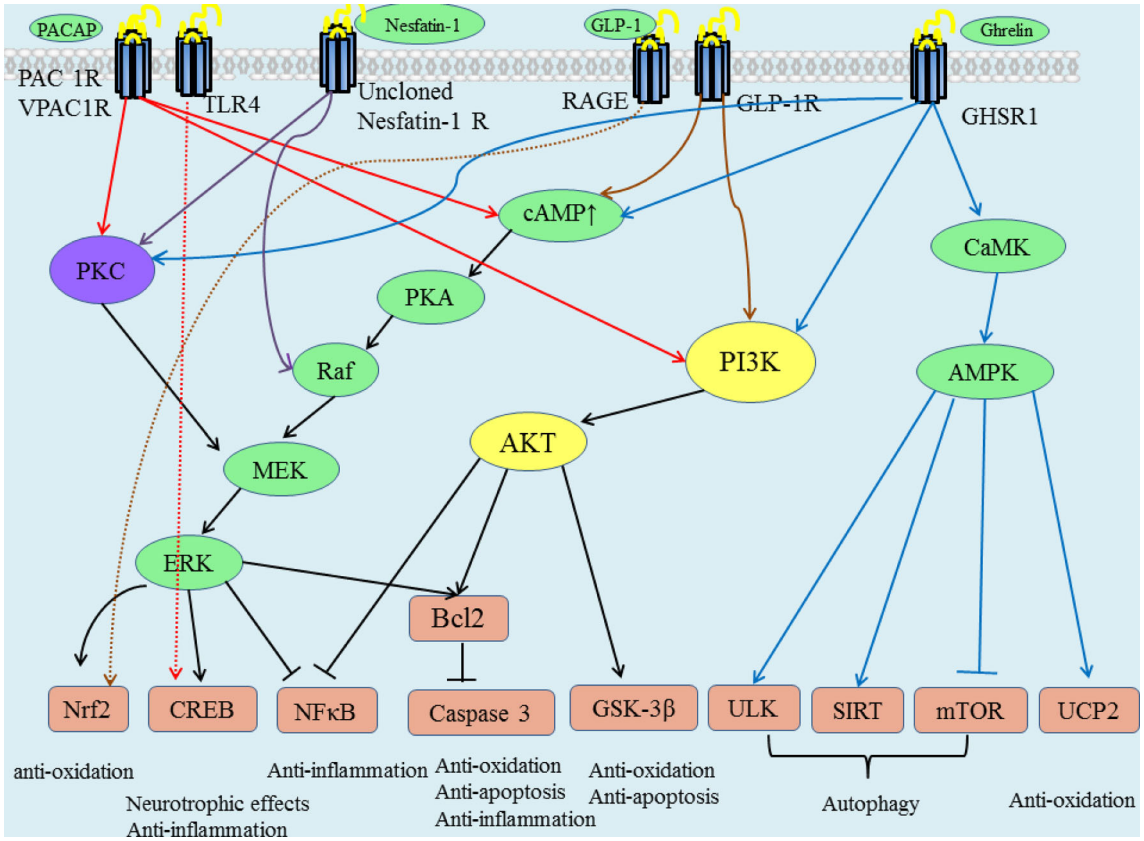

Fig. 1 The neuroprotective effects of the brain-gut peptides GLP-1, PACAP, nesfatin-1, and ghrelin, as well as related signaling pathways. PAC1R, PAC1 receptor; VPAC1R, VPAC1 receptor; TLR4, Toll-like receptor 4; RAGE, receptor for advanced glycation end product; GHSR1a, growth hormone secretagogue receptor 1a; nesfatin-1R, nesfatin-1 receptor; PKC, protein kinase C; cAMP, cyclic AMP; PKA, protein kinase A; MEK, mitogen-activated protein kinase kinase; ERK, extracellular regulated protein kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; Nrf2, nuclear factor erythroid 2-related factor 2; caspase 3, cysteinyl aspartate-cleaving protease 3; CREB, cAMP response element-binding protein; NFκB, nuclear factor-kappa B; Bcl2, B-cell lymphoma 2; GSK-3β, glycogen synthase kinase 3 beta; CaMK, CaM-dependent protein kinase; AMPK, AMP-activated protein kinase; ULK, Unc-51 like autophagy activating kinase; mTOR, mammalian target of rapamycin; SIRT, sirtuin; UCP2, uncoupling protein 2; ↓, activation; ⊥, inhibition; ⋮, many steps omitted.

pancreas [110]. The early secretion of PP induced by a meal is mediated by the vagus nerve, and has been suggested as a marker of vagal integrity. A recent study showed that PD patients have significantly decreased PP ratios after sham feeding compared with controls, suggesting that PP may be a marker of the presence of vagal denervation in early-to-moderate stage PD patients [111]. However, this conclusion is very controversial; another study [112] indicated that postprandial PP levels are normal in PD patients compared with the controls, suggesting that postprandial PP secretion is not a suitable marker of vagal nerve integrity in PD. The opposite conclusion may be due to differences in experimental methods. Besides, there is no enough evidence suggesting that PP has any neuroprotective effects on PD. Further research on the relationship between PP and PD is needed.

NT, a 13-amino-acid hormonal peptide, is present in the digestive system as well as in the CNS. The physiological functions of NT include stimulation of pancreatic and biliary secretion, inhibition of gastric and small bowel motility, stimulation of colonic motility, and a trophic effect on numerous tissues of the gastrointestinal tract. It also has various biological effects as a central neurotransmitter or neuromodulator, for example, the regulation of DA release [113].

Numerous studies [114, 115] have demonstrated that the NT receptor (NTR), in the substantia nigra of PD patients is dramatically lower than in controls, suggesting a NT-DA interaction in human nigro-striatal circuits and dysfunctional NTRs may be involved in PD. Also, a variety of studies [116] indicate that plasma NT concentrations in PD patients are consistently higher than in controls and PD patients treated with levodopa, which may be a compensatory mechanism for the loss of DA neurons to preserve motor function [117].

A study based on mouse models of PD have demonstrated that pretreatment with an NT analogue evidently decreases apomorphine-induced contralateral rotation and

D-amphetamine-induced ipsilateral rotation, suggesting anti-PD-like effects of NT [118]. Furthermore, in a recent study, the same neuroprotective effects of two new NT analogues, NT2 and NT4, have been reported inn rat models of PD, avoiding the rapid biodegradation of NT [119].

Interestingly, it has been shown that NT increases glutamate release and simultaneously amplifies the responsiveness of N-methyl-D-aspartate receptors (NMDARs), And the extracellular accumulation of glutamate and the excessive activation of NMDARs is known to be an important factor in the induction of the glutamate-mediated neuronal damage occurring in PD [120], so using NT receptor antagonists in the treatment of PD has been considered. However, in a randomized, double-blind, placebo-controlled study, the motor symptoms of PD did not improve after administration of the NT receptor antagonist SR 48692 [121].

In short, some studies suggest potential effects of NT for the treatment of PD, while the detailed mechanisms are still unclear, and the relationship between NT and PD are still not clear.

Conclusion

Numerous studies in vivo and in vitro have demonstrated that the four brain-gut peptides GLP-1, PACAP, nesfatin-1, and ghrelin play roles in neuroprotection and improve the motor symptoms of PD. Surprisingly, although different receptors are activated, these brain-gut peptides exert their neuroprotective effects through similar molecular mechanisms and signal pathways that are mainly involved in anti-inflammatory, anti-apoptotic, anti-oxidative, and neurotrophic effects. Moreover, analogues and receptor agonists of brain-gut peptides have been developed and used in clinical trials for PD. Further, various brain-gut peptides have been reported to participate in PD, suggesting a close link between dysfunction of the gut-brain axis and neurodegenerative diseases, providing a novel potential treatment strategy for PD.

In the future, multiple co-receptor agonists targeting different brain-gut peptide receptors in the brain may provide a promising treatment for PD. This requires further research into whether the combined application of multiple brain-gut peptides plays a synergistic role in neuroprotection. In addition, the precise mechanisms underlying the relationship between brain-gut peptides and the CNS need to be further elucidated.

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References

1. Lotankar S, Prabhavalkar KS, Bhatt LK. Biomarkers for Parkinson's disease: recent advancement. Neurosci Bull 2017, 33: 585–597.
2. Chen L, Xie J. Dopamine in Parkinson's disease: precise supplementation with motor planning. Neurosci Bull 2018, 34: 873–874.
3. Gan-Or Z, Alcalay RN, Rouleau GA, Postuma RB. Sleep disorders and Parkinson disease; lessons from genetics. Sleep Med Rev 2018.
4. Cersosimo MG, Benarroch EE. Pathological correlates of gastrointestinal dysfunction in Parkinson's disease. Neurobiol Dis 2012, 46: 559–564.
5. Lee S, Lee DY. Glucagon-like peptide-1 and glucagon-like peptide-1 receptor agonists in the treatment of type 2 diabetes. Ann Pediatr Endocrinol Metab 2017, 22: 15–26.
6. Athauda D, Foltynie T. Protective effects of the GLP-1 mimetic exendin-4 in Parkinson's disease. Neuropharmacology 2017.
7. Kim DS, Choi HI, Wang Y, Luo Y, Hoffer BJ, Greig NH. A new treatment strategy for Parkinson's disease through the gut-brain axis: the glucagon-like peptide-1 receptor pathway. Cell Transpl 2017, 26: 1560–1571.
8. Yildirim Simsir I, Soyaltin UE, Cetinkalp S. Glucagon like peptide-1 (GLP-1) likes Alzheimer's disease. Diabet Metab Syndr 2018, 12: 469–475.
9. Cantini G, Mannucci E, Luconi M. Perspectives in GLP-1 research: new targets, new receptors. Trends Endocrinol Metab 2016, 27: 427–438.
10. Santiago JA, Potashkin JA. System-based approaches to decode the molecular links in Parkinson's disease and diabetes. Neurobiol Dis 2014, 72 (Pt A):84–91.
11. De Pablo-Fernandez E, Goldacre R, Pakpoor J, Noyce AJ, Warner TT. Association between diabetes and subsequent Parkinson disease: a record-linkage cohort study. Neurology 2018, 91: e139–e142.
12. Egan AG, Blind E, Dunder K, de Graeff PA, Hummer BT, Bourcier T, *et al*. Pancreatic safety of incretin-based drugs–FDA and EMA assessment. N Engl J Med 2014, 370: 794–797.
13. Aksoy D, Solmaz V, Cavusoglu T, Meral A, Ates U, Erbas O. Neuroprotective effects of eexenatide in a rotenone-induced rat model of Parkinson's disease. Am J Med Sci 2017, 354: 319–324.
14. Badawi GA, Abd El Fattah MA, Zaki HF, El Sayed MI. Sitagliptin and liraglutide reversed nigrostriatal degeneration of rodent brain in rotenone-induced Parkinson's disease. Inflammopharmacology 2017, 25:369–382.
15. Nader MA, Ateyya H, El-Shafey M, El-Sherbeeny NA. Sitagliptin enhances the neuroprotective effect of pregabalin against pentylenetetrazole-induced acute epileptogenesis in mice: Implication of oxidative, inflammatory, apoptotic and autophagy pathways. Neurochem Int 2018, 115: 11–23.
16. Gault VA, Holscher C. GLP-1 receptor agonists show neuroprotective effects in animal models of diabetes. Peptides 2018, 100: 101–107.
17. Spielman LJ, Gibson DL, Klegeris A. Incretin hormones regulate microglia oxidative stress, survival and expression of trophic factors. Eur J Cell Biol 2017, 96: 240–253.
18. Khasnavis S, Jana A, Roy A, Mazumder M, Bhushan B, Wood T, *et al*. Suppression of nuclear factor-kappaB activation and inflammation in microglia by physically modified saline. J Biol Chem 2012, 287: 29529–29542.

19. Athauda D, Foltynie T. The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: mechanisms of action. Drug Discov Today 2016, 21: 802–818.
20. Bao Y, Jiang L, Chen H, Zou J, Liu Z, Shi Y. The Neuroprotective effect of liraglutide is mediated by glucagon-like peptide 1 receptor-mediated activation of cAMP/PKA/CREB pathway. Cell Physiol Biochem 2015, 36: 2366–2378.
21. An FM, Chen S, Xu Z, Yin L, Wang Y, Liu AR, *et al*. Glucagon-like peptide-1 regulates mitochondrial biogenesis and tau phosphorylation against advanced glycation end product-induced neuronal insult: Studies in vivo and in vitro. Neuroscience 2015, 300: 75–84.
22. Liu JH, Yin F, Guo LX, Deng XH, Hu YH. Neuroprotection of geniposide against hydrogen peroxide induced PC12 cells injury: involvement of PI3 kinase signal pathway. Acta Pharmacol Sin 2009, 30: 159–165.
23. Liu J, Yin F, Zheng X, Jing J, Hu Y. Geniposide, a novel agonist for GLP-1 receptor, prevents PC12 cells from oxidative damage via MAP kinase pathway. Neurochem Int 2007, 51: 361–369.
24. Fernandez-Millan E, Martin MA, Goya L, Lizarraga-Mollinedo E, Escriva F, Ramos S, *et al*. Glucagon-like peptide-1 improves beta-cell antioxidant capacity via extracellular regulated kinases pathway and Nrf2 translocation. Free Radic Biol Med 2016, 95: 16–26.
25. Abdelsalam RM, Safar MM. Neuroprotective effects of vildagliptin in rat rotenone Parkinson's disease model: role of RAGE-NFkappaB and Nrf2-antioxidant signaling pathways. J Neurochem 2015, 133: 700–707.
26. Zhu H, Zhang Y, Shi Z, Lu D, Li T, Ding Y, *et al*. The neuroprotection of liraglutide against ischaemia-induced apoptosis through the activation of the PI3K/AKT and MAPK pathways. Sci Rep 2016, 6: 26859.
27. Li Y, Tweedie D, Mattson MP, Holloway HW, Greig NH. Enhancing the GLP-1 receptor signaling pathway leads to proliferation and neuroprotection in human neuroblastoma cells. J Neurochem 2010, 113: 1621–1631.
28. Li M, Li S, Li Y. Liraglutide Promotes cortical neurite outgrowth via the MEK-ERK pathway. Cell Mol Neurobiol 2015, 35: 987–993.
29. Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Ell P, Soderlund T, *et al*. Exenatide and the treatment of patients with Parkinson's disease. J Clin Invest 2013, 123: 2730–2736.
30. Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Kahan J, Ell P, *et al*. Motor and cognitive advantages persist 12 months after exenatide exposure in Parkinson's disease. J Parkinsons Dis 2014, 4: 337–344.
31. Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, *et al*. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet 2017, 390: 1664–1675.
32. Holscher C. Novel dual GLP-1/GIP receptor agonists show neuroprotective effects in Alzheimer's and Parkinson's disease models. Neuropharmacology 2018,136(Pt B): 251–259.
33. Vaudry D, Falluel-Morel A, Bourgault S, Basille M, Burel D, Wurtz O, *et al*. Pituitary adenylate cyclase-activating polypeptide and its receptors: 20 years after the discovery. Pharmacol Rev 2009, 61: 283–357.
34. Amin FM, Schytz HW. Transport of the pituitary adenylate cyclase-activating polypeptide across the blood-brain barrier: implications for migraine. J Headache Pain 2018, 19: 35.
35. Reglodi D, Illes A, Opper B, Schafer E, Tamas A, Horvath G. Presence and effects of pituitary adenylate cyclase activating polypeptide under physiological and pathological conditions in the stomach. Front Endocrinol (Lausanne) 2018, 9: 90.
36. Watson MB, Nobuta H, Abad C, Lee SK, Bala N, Zhu C, *et al*. PACAP deficiency sensitizes nigrostriatal dopaminergic neurons to paraquat-induced damage and modulates central and peripheral inflammatory activation in mice. Neuroscience 2013, 240: 277–286.
37. Reglodi D, Kiss P, Lubics A, Tamas A. Review on the protective effects of PACAP in models of neurodegenerative diseases in vitro and in vivo. Curr Pharm Des 2011, 17: 962–972.
38. Reglodi D, Renaud J, Tamas A, Tizabi Y, Socias SB, Del-Bel E, *et al*. Novel tactics for neuroprotection in Parkinson's disease: Role of antibiotics, polyphenols and neuropeptides. Dis Model Mech 2017, 155: 120–148.
39. Reglodi D, Tamas A, Jungling A, Vaczy A, Rivnyak A, Fulop BD, *et al*. Protective effects of pituitary adenylate cyclase activating polypeptide against neurotoxic agents. Neurotoxicology 2018, 66: 185–194.
40. Poujol de Molliens M, Letourneau M, Devost D, Hebert TE, Fournier A, Chatenet D. New insights about the peculiar role of the 28–38 C-terminal segment and some selected residues in PACAP for signaling and neuroprotection. Biochem Pharmacol 2018, 154:193–202.
41. Lamine A, Letourneau M, Doan ND, Maucotel J, Couvineau A, Vaudry H, *et al*. Characterizations of a synthetic pituitary adenylate cyclase-activating polypeptide analog displaying potent neuroprotective activity and reduced in vivo cardiovascular side effects in a Parkinson's disease model. Neuropharmacology 2016, 108: 440–450.
42. Lee EH, Seo SR. Neuroprotective roles of pituitary adenylate cyclase-activating polypeptide in neurodegenerative diseases. BMB Rep 2014, 47: 369–375.
43. Wang G, Qi C, Fan GH, Zhou HY, Chen SD. PACAP protects neuronal differentiated PC12 cells against the neurotoxicity induced by a mitochondrial complex I inhibitor, rotenone. FEBS Lett 2005, 579: 4005–4011.
44. Bhave SV, Hoffman PL. Phosphatidylinositol 3′-OH kinase and protein kinase A pathways mediate the anti-apoptotic effect of pituitary adenylyl cyclase-activating polypeptide in cultured cerebellar granule neurons: modulation by ethanol. J Neurochem 2004, 88: 359–369.
45. Cabezas R, Baez-Jurado E, Hidalgo-Lanussa O, Echeverria V, Ashrad GM, Sahebkar A, *et al*. Growth factors and neuroglobin in astrocyte protection against neurodegeneration and oxidative stress. Mol Neurobiol 2019, 56: 2339–2351.
46. Masmoudi-Kouki O, Douiri S, Hamdi Y, Kaddour H, Bahdoudi S, Vaudry D, *et al*. Pituitary adenylate cyclase-activating polypeptide protects astroglial cells against oxidative stress-induced apoptosis. J Neurochem 2011, 117: 403–411.
47. Douiri S, Bahdoudi S, Hamdi Y, Cubi R, Basille M, Fournier A, *et al*. Involvement of endogenous antioxidant systems in the protective activity of pituitary adenylate cyclase-activating polypeptide against hydrogen peroxide-induced oxidative damages in cultured rat astrocytes. J Neurochem 2016, 137: 913–930.
48. Cheng HH, Ye H, Peng RP, Deng J, Ding Y. Inhibition of retinal ganglion cell apoptosis: regulation of mitochondrial function by PACAP. Neural Regen Res 2018, 13: 923–929.
49. Joshi N, Singh S. Updates on immunity and inflammation in Parkinson disease pathology. J Neurosci Res 2018, 96: 379–390.
50. Waschek JA. VIP and PACAP: neuropeptide modulators of CNS inflammation, injury, and repair. Br J Pharmacol 2013, 169: 512–523.
51. Elekes K, Sandor K, Moricz A, Kereskai L, Kemeny A, Szoke E, *et al*. Pituitary adenylate cyclase-activating polypeptide plays an anti-inflammatory role in endotoxin-induced airway inflammation: in vivo study with gene-deleted mice. Peptides 2011, 32: 1439–1446.

52. Nedvig K, Szabo G, Csukas D, Sandor J, Nemeth J, Kovacs K, *et al*. Examination of cytoprotective and anti-inflammatory effect of PACAP-38 on small bowel autotransplantation. Magy Seb 2013, 66: 250–255.
53. Sakamoto K, Kuno K, Takemoto M, He P, Ishikawa T, Onishi S, *et al*. Pituitary adenylate cyclase-activating polypeptide protects glomerular podocytes from inflammatory injuries. J Diabetes Res 2015, 2015: 727152.
54. Brown D, Tamas A, Reglodi D, Tizabi Y. PACAP protects against inflammatory-mediated toxicity in dopaminergic SH-SY5Y cells: implication for Parkinson's disease. Neurotox Res 2014, 26: 230–239.
55. Qin X, Sun ZQ, Dai XJ, Mao SS, Zhang JL, Jia MX, *et al*. Toll-like receptor 4 signaling is involved in PACAP-induced neuroprotection in BV2 microglial cells under OGD/reoxygenation. Neurol Res 2012, 34: 379–389.
56. Brown D, Tamas A, Reglodi D, Tizabi Y. PACAP protects against salsolinol-induced toxicity in dopaminergic SH-SY5Y cells: implication for Parkinson's disease. J Mol Neurosci 2013, 50: 600–607.
57. Fukuchi M, Tabuchi A, Kuwana Y, Watanabe S, Inoue M, Takasaki I, *et al*. Neuromodulatory effect of Galphas- or Galphaq-coupled G-protein-coupled receptor on NMDA receptor selectively activates the NMDA receptor/Ca^{2+}/calcineurin/cAMP response element-binding protein-regulated transcriptional coactivator 1 pathway to effectively induce brain-derived neurotrophic factor expression in neurons. J Neurosci 2015, 35: 5606–5624.
58. Oh IS, Shimizu H, Satoh T, Okada S, Adachi S, Inoue K, *et al*. Identification of nesfatin-1 as a satiety molecule in the hypothalamus. Nature 2006, 443: 709–712.
59. Goebel-Stengel M, Wang L. Central and peripheral expression and distribution of NUCB2/nesfatin-1. Curr Pharm Des 2013, 19: 6935–6940.
60. Price TO, Samson WK, Niehoff ML, Banks WA. Permeability of the blood-brain barrier to a novel satiety molecule nesfatin-1. Peptides 2007, 28: 2372–2381.
61. Ozcan M, Gok ZB, Kacar E, Serhatlioglu I, Kelestimur H. Nesfatin-1 increases intracellular calcium concentration by protein kinase C activation in cultured rat dorsal root ganglion neurons. Neurosci Lett 2016, 619: 177–181.
62. Ishida E, Hashimoto K, Shimizu H, Okada S, Satoh T, Kato I, *et al*. Nesfatin-1 induces the phosphorylation levels of cAMP response element-binding protein for intracellular signaling in a neural cell line. PLoS ONE 2012, 7: e50918.
63. Dore R, Levata L, Lehnert H, Schulz C. Nesfatin-1: functions and physiology of a novel regulatory peptide. J Endocrinol 2017, 232: R45–R65.
64. Li C, Zhang F, Shi L, Zhang H, Tian Z, Xie J, *et al*. Nesfatin-1 decreases excitability of dopaminergic neurons in the substantia nigra. J Mol Neurosci 2014, 52: 419–424.
65. Sulzer D. Multiple hit hypotheses for dopamine neuron loss in Parkinson's disease. Trends Neurosci 2007, 30: 244–250.
66. Shen XL, Song N, Du XX, Li Y, Xie JX, Jiang H. Nesfatin-1 protects dopaminergic neurons against MPP(+)/MPTP-induced neurotoxicity through the C-Raf-ERK1/2-dependent anti-apoptotic pathway. Sci Rep 2017, 7: 40961.
67. Tang CH, Fu XJ, Xu XL, Wei XJ, Pan HS. The anti-inflammatory and anti-apoptotic effects of nesfatin-1 in the traumatic rat brain. Peptides 2012, 36: 39–45.
68. Ozsavci D, Ersahin M, Sener A, Ozakpinar OB, Toklu HZ, Akakin D, *et al*. The novel function of nesfatin-1 as an anti-inflammatory and antiapoptotic peptide in subarachnoid hemorrhage-induced oxidative brain damage in rats. Neurosurgery 2011, 68: 1699–1708.
69. Kowaltowski AJ, Castilho RF, Vercesi AE. Mitochondrial permeability transition and oxidative stress. FEBS Lett 2001, 495: 12–15.
70. Tan Z, Xu H, Shen X, Jiang H. Nesfatin-1 antagonized rotenone-induced neurotoxicity in MES23.5 dopaminergic cells. Peptides 2015, 69:109–114.
71. Erfani S, Moghimi A, Aboutaleb N, Khaksari M. Protective effects of Nesfatin-1 peptide on cerebral ischemia reperfusion injury via inhibition of neuronal cell death and enhancement of antioxidant defenses. Metab Brain Dis 2018.
72. Brailoiu GC, Dun SL, Brailoiu E, Inan S, Yang J, Chang JK, *et al*. Nesfatin-1: distribution and interaction with a G protein-coupled receptor in the rat brain. Endocrinology 2007, 148: 5088–5094.
73. Ge JF, Xu YY, Qin G, Pan XY, Cheng JQ, Chen FH. Nesfatin-1, a potent anorexic agent, decreases exploration and induces anxiety-like behavior in rats without altering learning or memory. Brain Res 2015, 1629: 171–181.
74. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999, 402: 656–660.
75. Müller TD, Nogueiras R, Andermann ML, Andrews ZB, Anker SD, Argente J, *et al*. Ghrelin. Mol Metab 2015, 4: 437–460.
76. Hosoda H, Kojima M, Matsuo H, Kangawa K. Ghrelin and des-acyl ghrelin: two major forms of rat ghrelin peptide in gastrointestinal tissue. Biochem Biophys Res Commun 2000, 279: 909–913.
77. Banks WA, Tschop M, Robinson SM, Heiman ML. Extent and direction of ghrelin transport across the blood-brain barrier is determined by its unique primary structure. J Pharmacol Exp Ther 2002, 302: 822–827.
78. Suda Y, Kuzumaki N, Sone T, Narita M, Tanaka K, Hamada Y, *et al*. Down-regulation of ghrelin receptors on dopaminergic neurons in the substantia nigra contributes to Parkinson's disease-like motor dysfunction. Mol Brain 2018, 11: 6.
79. Unger MM, Moller JC, Mankel K, Eggert KM, Bohne K, Bodden M, *et al*. Postprandial ghrelin response is reduced in patients with Parkinson's disease and idiopathic REM sleep behaviour disorder: a peripheral biomarker for early Parkinson's disease? J Neurol 2011, 258: 982–990.
80. Song N, Wang W, Jia F, Du X, Xie A, He Q, *et al*. Assessments of plasma ghrelin levels in the early stages of parkinson's disease. Mov Disord 2017, 32: 1487–1491.
81. Karasawa H, Pietra C, Giuliano C, Garcia-Rubio S, Xu X, Yakabi S, *et al*. New ghrelin agonist, HM01 alleviates constipation and L-dopa-delayed gastric emptying in 6-hydroxydopamine rat model of Parkinson's disease. Neurogastroenterol Motil 2014, 26: 1771–1782.
82. Shi L, Bian X, Qu Z, Ma Z, Zhou Y, Wang K, *et al*. Peptide hormone ghrelin enhances neuronal excitability by inhibition of Kv7/KCNQ channels. Nat Commun 2013, 4: 1435.
83. Liu H, Jia L, Chen X, Shi L, Xie J. The Kv7/KCNQ channel blocker XE991 protects nigral dopaminergic neurons in the 6-hydroxydopamine rat model of Parkinson's disease. Brain Res Bull 2018, 137: 132–139.
84. Bayliss JA, Lemus M, Santos VV, Deo M, Elsworth JD, Andrews ZB. Acylated but not des-acyl ghrelin is neuroprotective in an MPTP mouse model of Parkinson's disease. J Neurochem 2016, 137: 460–471.
85. Bayliss JA, Lemus MB, Stark R, Santos VV, Thompson A, Rees DJ, *et al*. Ghrelin-AMPK signaling mediates the neuroprotective effects of calorie restriction in Parkinson's disease. J Neurosci 2016, 36: 3049–3063.
86. Moon M, Kim HG, Hwang L, Seo JH, Kim S, Hwang S, *et al*. Neuroprotective effect of ghrelin in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease

by blocking microglial activation. Neurotox Res 2009, 15: 332–347.
87. Jiang H, Li LJ, Wang J, Xie JX. Ghrelin antagonizes MPTP-induced neurotoxicity to the dopaminergic neurons in mouse substantia nigra. Exp Neurol 2008, 212: 532–537.
88. Chung H, Seo S, Moon M, Park S. Phosphatidylinositol-3-kinase/Akt/glycogen synthase kinase-3 beta and ERK1/2 pathways mediate protective effects of acylated and unacylated ghrelin against oxygen-glucose deprivation-induced apoptosis in primary rat cortical neuronal cells. J Endocrinol 2008, 198: 511–521.
89. Chung H, Kim E, Lee DH, Seo S, Ju S, Lee D, *et al*. Ghrelin inhibits apoptosis in hypothalamic neuronal cells during oxygen-glucose deprivation. Endocrinol 2007, 148: 148–159.
90. Ishii N, Tsubouchi H, Miura A, Yanagi S, Ueno H, Shiomi K, *et al*. Ghrelin alleviates paclitaxel-induced peripheral neuropathy by reducing oxidative stress and enhancing mitochondrial anti-oxidant functions in mice. Eur J Pharmacol 2018, 819: 35–42.
91. Andrews ZB, Erion D, Beiler R, Liu ZW, Abizaid A, Zigman J, *et al*. Ghrelin promotes and protects nigrostriatal dopamine function via a UCP2-dependent mitochondrial mechanism. J Neurosci 2009, 29: 14057–14065.
92. Lopez NE, Gaston L, Lopez KR, Coimbra RC, Hageny A, Putnam J, *et al*. Early ghrelin treatment attenuates disruption of the blood brain barrier and apoptosis after traumatic brain injury through a UCP-2 mechanism. Brain Res 2012, 1489: 140–148.
93. Liu L, Xu H, Jiang H, Wang J, Song N, Xie J. Ghrelin prevents 1-methyl-4-phenylpyridinium ion-induced cytotoxicity through antioxidation and NF-kappaB modulation in MES23.5 cells. Exp Neurol 2010, 222: 25–29.
94. Morgan AH, Rees DJ, Andrews ZB, Davies JS. Ghrelin mediated neuroprotection—A possible therapy for Parkinson's disease? Neuropharmacology 2018, 136: 317–326.
95. Srivastava S, Haigis MC. Role of sirtuins and calorie restriction in neuroprotection: implications in Alzheimer's and Parkinson's diseases. Curr Pharm Des 2011, 17: 3418–3433.
96. Ferreira-Marques M, Aveleira CA, Carmo-Silva S, Botelho M, Pereira de Almeida L, Cavadas C. Caloric restriction stimulates autophagy in rat cortical neurons through neuropeptide Y and ghrelin receptors activation. Aging (Albany NY) 2016, 8: 1470–1484.
97. Mao Y, Cheng J, Yu F, Li H, Guo C, Fan X. Ghrelin attenuated lipotoxicity via autophagy induction and nuclear factor-kappaB inhibition. Cell Physiol Biochem 2015, 37: 563–576.
98. Wan SX, Shi B, Lou XL, Liu JQ, Ma GG, Liang DY, *et al*. Ghrelin protects small intestinal epithelium against sepsis-induced injury by enhancing the autophagy of intestinal epithelial cells. Biomed Pharmacother 2016, 83: 1315–1320.
99. Xu M, Liu L, Song C, Chen W, Gui S. Ghrelin improves vascular autophagy in rats with vascular calcification. Life Sci 2017, 179: 23–29.
100. Bayliss JA, Andrews ZB. Ghrelin is neuroprotective in Parkinson's disease: molecular mechanisms of metabolic neuroprotection. Ther Adv Endocrinol Metab 2013, 4: 25–36.
101. Kim J, Kundu M, Viollet B, Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol 2011, 13: 132–141.
102. Han K, Wang QY, Wang CX, Luan SY, Tian WP, Wang Y, *et al*. Ghrelin improves pilocarpineinduced cerebral cortex inflammation in epileptic rats by inhibiting NFkappaB and TNFalpha. Mol Med Rep 2018, 18: 3563–3568.
103. Beynon AL, Brown MR, Wright R, Rees MI, Sheldon IM, Davies JS. Ghrelin inhibits LPS-induced release of IL-6 from mouse dopaminergic neurones. J Neuroinflamm 2013, 10: 40.
104. Frago LM, Chowen JA. Involvement of astrocytes in mediating the central effects of ghrelin. Int J Mol Sci 2017, 18: E536. https://doi.org/10.3390/ijms18030536.
105. Kent BA, Beynon AL, Hornsby AK, Bekinschtein P, Bussey TJ, Davies JS, *et al*. The orexigenic hormone acyl-ghrelin increases adult hippocampal neurogenesis and enhances pattern separation. Psychoneuroendocrinology 2015, 51: 431–439.
106. Sato M, Nakahara K, Goto S, Kaiya H, Miyazato M, Date Y, *et al*. Effects of ghrelin and des-acyl ghrelin on neurogenesis of the rat fetal spinal cord. Biochem Biophys Res Commun 2006, 350: 598–603.
107. Maswood N, Young J, Tilmont E, Zhang Z, Gash DM, Gerhardt GA, *et al*. Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease. Proc Natl Acad Sci U S A 2004, 101: 18171–18176.
108. Korkmaz OT, Tuncel N. Advantages of Vasoactive Intestinal peptide for the future treatment of Parkinson's disease. Curr Pharm Des 2018, 24: 4693–4701.
109. Hirabayashi T, Nakamachi T, Shioda S. Discovery of PACAP and its receptors in the brain. J Headache Pain 2018, 19: 28.
110. Lonovics J, Devitt P, Watson LC, Rayford PL, Thompson JC. Pancreatic polypeptide. A review. Arch Surg 1981, 116: 1256–1264.
111. Knudsen K, Hartmann B, Fedorova TD, Ostergaard K, Krogh K, Moller N, *et al*. Pancreatic polypeptide in Parkinson's disease: A potential marker of parasympathetic denervation. J Parkinsons Dis 2017, 7: 645–652.
112. Unger MM, Ekman R, Bjorklund AK, Karlsson G, Andersson C, Mankel K, *et al*. Unimpaired postprandial pancreatic polypeptide secretion in Parkinson's disease and REM sleep behavior disorder. Mov Disord 2013, 28: 529–533.
113. Kulinska-Niedziela I, Paluszak J. Neurotensin–structure, origin and biological function. Postepy Hig Med Dosw 1997, 51: 329–342.
114. Chinaglia G, Probst A, Palacios JM. Neurotensin receptors in Parkinson's disease and progressive supranuclear palsy: an autoradiographic study in basal ganglia. Neuroscience 1990, 39: 351–360.
115. Uhl GR, Whitehouse PJ, Price DL, Tourtelotte WW, Kuhar MJ. Parkinson's disease: depletion of substantia nigra neurotensin receptors. Brain Res 1984, 308: 186–190.
116. Schimpff RM, Avard C, Fenelon G, Lhiaubet AM, Tenneze L, Vidailhet M, *et al*. Increased plasma neurotensin concentrations in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2001, 70: 784–786.
117. Boules M, Li Z, Smith K, Fredrickson P, Richelson E. Diverse roles of neurotensin agonists in the central nervous system. Front Endocrinol (Lausanne) 2013, 4: 36.
118. Boules M, Warrington L, Fauq A, McCormick D, Richelson E. Antiparkinson-like effects of a novel neurotensin analog in unilaterally 6-hydroxydopamine lesioned rats. Eur J Pharmacol 2001, 428: 227–233.
119. Lazarova M, Popatanasov A, Klissurov R, Stoeva S, Pajpanova T. Preventive effect of two new neurotensin analogues on Parkinson's disease rat model. J Mol Neurosci 2018, 66: 552–560.
120. Ferraro L, Tomasini MC, Beggiato S, Guerrini R, Salvadori S, Fuxe K, *et al*. Emerging evidence for neurotensin receptor 1 antagonists as novel pharmaceutics in neurodegenerative disorders. Mini Rev Med Chem 2009, 9: 1429–1438.
121. Mesnage V, Houeto JL, Bonnet AM, Clavier I, Arnulf I, Cattelin F, *et al*. Neurokinin B, neurotensin, and cannabinoid receptor antagonists and Parkinson disease. Clin Neuropharmacol 2004, 27: 108–110.