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Ghrelin-based interventions in preclinical models of Parkinson's disease: a systematic review

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Abbreviations: 6-OHDA, Neurotoxin inducing selective dopaminergic neuron loss, PD model; α-synuclein/αS, Protein forming Lewy bodies, hallmark of PD; Acylated ghrelin, Active form of ghrelin; AMPK/pAMPK, Energy sensor regulating metabolism and autophagy; Astrocytes, Central nervous system support cells; Atg7, Autophagy-related enzyme required for autophagosome formation.; Bax, Pro-apoptotic mitochondrial protein; Bcl-2, Anti-apoptotic mitochondrial protein; Beclin1, Key initiator of autophagy; Caspase-3/Cleaved caspase-3, Effector enzyme of apoptosis; Caspase-12/Cleaved caspase-12, Endoplasmic reticulum stress-mediated apoptosis enzyme; c-Fos/Fos-ir, Immediate early gene protein, marker of neuronal activation; ChAT, Enzyme synthesizing acetylcholine marker of cholinergic neurons; CHOP, C/EBP homologous protein mediating endoplasmic reticulum stress-induced apoptosis; COMT, Catechol-O-methyltransferase, enzyme metabolizing dopamine; Corticosterone, Stress hormone; CPT1, Carnitine palmitoyltransferase 1, mitochondrial enzyme for fatty acid transport; DA, Dopamine, key neurotransmitter in the dopaminergic system; DAT, Dopamine transporter; Des-acylated ghrelin, Inactive form of ghrelin; DOPAC, 3,4-Dihydroxyphenylacetic acid, dopamine metabolite; DOPAC/DA ratio, Indicator of dopamine turnover; ERS, Endoplasmic reticulum stress; GHSR-1a, Growth hormone secretagogue receptor type 1a, receptor for acylated ghrelin; GRP78, Endoplasmic reticulum chaperone regulating the unfolded protein response; HM01, Synthetic ghrelin receptor agonist; HVA, Homovanillic acid, final dopamine metabolite; ICV, Intracerebroventricular administration; IL-1β, IL-6, Pro-inflammatory interleukins; IL-10, Anti-inflammatory interleukin; iNOS, Inducible nitric oxide synthase, inflammatory mediator; IP, Intraperitoneal administration; LC3B-II/LC3 II, Lipidated LC3, autophagy marker; LRRK2/GBA1, Genes associated with Parkinson's disease risk; MAO-B, Monoamine oxidase B, dopamine-metabolizing enzyme; MFB, Medial forebrain bundle, dopaminergic fiber tract; Microglia, Resident immune cells of the central nervous system; MMP-3, Matrix metalloproteinase-3, protease contributing to neuroinflammation; MPP+, Active neurotoxic metabolite of MPTP; MPTP, Neurotoxin inducing dopaminergic degeneration, PD model; NEFA, Non-esterified fatty acids in plasma; Nitrotyrosine-positive neurons, Neurons exhibiting oxidative stress markers; p-ASK1, Phosphorylated apoptosis signal-regulating kinase 1; p-IRE1α, Phosphorylated inositol-requiring enzyme 1 alpha, ER stress sensor; p-JNK, Phosphorylated Jun N-terminal kinase involved in stress and apoptosis signaling; p62, Autophagy adaptor protein degraded during autophagy; PDI, Peripheral dopa-decarboxylase inhibitor.; Phosphorylated α-synuclein/p-αS, Pathological phosphorylated form of α-synuclein; pACC/ACC, Acetyl-CoA carboxylase regulating lipid metabolism; Rota-rod, Test of motor coordination and balance; ROS, Reactive oxygen species; Rotations/Contralateral paw use, Measures of asymmetric motor behavior after lesion; SN/SNpc, Substantia nigra pars compacta, region densely populated by dopaminergic neurons; SOD1, Antioxidant enzyme superoxide dismutase 1; Striatal TH fibers, Dopaminergic fibers in the striatum; TFEB, Transcription factor regulating autophagy and lysosomal biogenesis; TH, Tyrosine hydroxylase, rate-limiting enzyme in dopamine synthesis; TH-ir/TH-positive cells, Dopaminergic neurons identified by TH immunoreactivity; TH protein expression, Levels of TH protein in the substantia nigra and striatum; TNF-α, Pro-inflammatory cytokine; UCP-2, Mitochondrial uncoupling protein reducing reactive oxygen species production; XBP1s, Spliced X-box binding protein 1, mediator of the unfolded protein response.

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ABSTRACT

Ghrelin plays a crucial role in metabolism and gastrointestinal function. In the central nervous system, ghrelin modulates both hedonic and homeostatic control of eating behavior. Ghrelin promotes neuron survival by reducing apoptosis, inflammation, and oxidative stress, making it a potential therapeutic agent for neurodegenerative diseases. Parkinson's Disease (PD) is a neurodegenerative disease characterized by motor and non-motor symptoms. The motor impairments result primarily from the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta. Individuals with PD exhibit reduced levels of fasting and postprandial plasma ghrelin, and its receptors (GHSR) are expressed in the substantia nigra. Thus, this review aimed to evaluate the effects of ghrelin or GHSR agonists administration in experimental models of PD. A systematic search was conducted across PubMed, Scopus, Web of Science, and Embase. The 12 included studies involved PD models induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), as well as A53T transgenic mice. Interventions were performed with acylated and/or des-acylated ghrelin, in addition to the GHSR agonist HM01. Intervention with ghrelin was able to reduce dopaminergic neurodegeneration and improve motor function, while also positively impacting metabolic and gastrointestinal functions, expanding its relevance to non-motor consequences of PD. Considering that most results were obtained using acute toxin-induced models and only male animals, further studies using progressive PD models and evaluating sex differences are needed. Thus, although preclinical evidence supports ghrelin or GHSR agonists as promising agents for treatment, future studies will be essential to inform clinical translation and optimize therapeutic strategies for individuals with PD.

1. Introduction

Ghrelin, a peptide hormone predominantly produced by the stomach, was identified in 1999 as the endogenous ligand for the growth hormone secretagogue receptor (GHSR) 1a (Kojima et al., 1999). In subsequent years, discoveries were made regarding the peripheral and central effects of ghrelin. In the gastrointestinal system, ghrelin plays a crucial role in regulating glucose and lipid metabolism, while also protecting the mucosa and controlling gastrointestinal motility (Asakawa et al., 2001; Koutouratsas et al., 2019; Masuda et al., 2000). In skeletal muscle, its effects are associated with blocking atrophy through pathways independent of the growth hormone (Filigheddu et al., 2007; Porporato et al., 2013). In the central nervous system, ghrelin acts by modulating the hedonic and homeostatic control of eating behavior, influencing both food reactivity and neuropeptide secretion (Han et al., 2018; Mason et al., 2014; Tschop et al., 2000). In addition, ghrelin can increase neuron survival by reducing apoptosis, inflammation, and oxidative stress (Jiao et al., 2017). In this context, ghrelin emerges as an alternative treatment for several neurodegenerative conditions, including Parkinson's disease (PD).

PD is a neurodegenerative disease characterized by motor and non-motor symptoms. While motor symptoms include rigidity, tremors, and bradykinesia, non-motor symptoms comprise psychiatric disorders, as well as gastrointestinal and olfactory dysfunctions (Armstrong and Okun, 2020; Chaudhuri et al., 2006; Maia et al., 2025). The motor impairments result primarily from the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) (Jiang et al., 2008). Considered the fastest-growing neurological disorder in the world, the global number of cases is predicted to reach 25.2 million by 2050, representing a 112% increase compared to 2021 (Su et al., 2025). As a result, therapeutic interventions for PD are continuously expanding. Currently, effective and possibly effective treatments include levodopa/peripheral dopa-decarboxylase inhibitor (PDI), dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase B (MAO-B) inhibitors, and surgery (de Bie et al., 2025). Reductions in fasting and postprandial plasma concentrations of ghrelin, however, have been observed in individuals with PD (Gouveia et al., 2025), and GHSRs have been widely found in the SNpc (Zigman et al., 2006). Consequently, the administration of ghrelin or GHSR agonists may serve as a potential treatment for reducing the peripheral and central damage observed in experimental PD models.

To test this, several experimental models have been used, in particular models where ghrelin-induced neuroprotection was assessed after the induction of mitochondrial damage. The options involved toxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), paraquat/maneb, rotenone, trichloroethylene, or homocysteine, which can induce some of the neuropathological and behavioral features of PD, including neuronal loss, striatal dopamine (DA) depletion, and/or motor behavior, although not all of these models induce α-synuclein pathology (Jiang and Dickson, 2018). Other models, in turn, involved knockout animals, as well as transgenic cell lines compared with wild-type controls (Jiang and Dickson, 2018). The treatments with ghrelin included interventions with its active form, acylated ghrelin, and inactive form, des-acylated ghrelin, at different doses and routes of administration, in addition to the use of synthetic agonists such as HM01 (Andrews et al., 2009; Bayliss et al., 2016a,b; Rees et al., 2023).

This review aims to evaluate the effects of ghrelin or GHSR agonists administration in experimental models of PD. Considering its wide range of action in peripheral and central systems, all outcomes were evaluated. Thus, this review systematically compiled and analyzed the preclinical data currently available and contributes to the global understanding of the mechanisms involved in controlling PD symptoms, with the potential to guide clinical studies and, consequently, promote the overall well-being of people living with PD.

2. Methods

2.1. Literature search strategy

Two independent reviewers (HJCBG and OHSJ) accessed Scopus, Medline/PubMed, Web of Science, and Embase databases using the search descriptors described below. The databases were consulted in July 2025. The PICO strategy was adopted, establishing the terms of interest based on the "population" and "intervention" components. The following descriptors were used for the population: "Parkinson Disease [MeSH]" OR "Parkinsonian Disorders [MeSH]" OR "Parkinson's Disease [non-MeSH]". For the intervention, we used "Ghrelin [MeSH]". In each database, we combined the population and intervention terms using the Boolean operator "AND", and exported the articles found to the Rayyan platform (https://new.rayyan.ai/). A third reviewer was consulted in cases of disagreement regarding study inclusion (JPSJ). The protocol for this review is published in the international prospective register of systematic reviews (PROSPERO) database (ID: CRD420251106272).

2.2. Study selection and data extraction

In the first phase, the studies were selected by two reviewers (HJCBG

and OHSJ) after reading the titles and abstracts. At this stage, we applied the following exclusion criteria: non-original studies (e.g. reviews, editorials and abstracts); studies with designs not aligned with the review objectives; studies involving the use of non-animal models; studies involving interventions unrelated to ghrelin/GHSR agonists. After this initial examination, the studies were assessed for eligibility after full reading. Studies with an inappropriate design were excluded. We included studies in animal models of PD that administered exogenous ghrelin or GHSR receptor agonists, but excluded studies or groups where the animals received pharmacological or behavioral interventions in combination with the main treatment or used models to test the effects of endogenous ghrelin. We also excluded studies where the animals had conditions other than PD. Articles were not restricted in terms of year of publication or language. A third reviewer was consulted in cases of disagreement in each of the two phases (JPSJ).

The data extraction stage was also carried out by two reviewers (HJCBG and OHSJ) with the assistance of a third to review the data collected (JPSJ). Regarding the characteristics of the studies, we extracted data from: authors, experimental groups, sex and age of the animals, and characteristics of the intervention, including details on the PD experimental model used and, on the ghrelin, or GHSR agonist intervention (dose, route, and duration). Regarding the outcomes, we collected all the results that were presented with comparisons between the control, PD, and PD with intervention (ghrelin or GHSR agonists) groups. Therefore, parameters that were presented only with the effects caused by the experimental PD model, without evaluating the effects of the intervention with ghrelin or agonists, were not included. The number of animals used for each outcome was also extracted. A qualitative (narrative) synthesis was performed considering the methodological and clinical heterogeneity of the included studies, which prevented the performance of a *meta*-analysis.

2.3. Analysis of risk bias in individual studies

The risk of bias in the included studies was assessed using SYRCLE's Risk of Bias tool for animal studies. The tool evaluates seven different domains: selection bias (sequence generation, baseline characteristics, and allocation concealment); performance bias (random housing and blinding); detection bias (random outcome assessment and blinding); attrition bias (incomplete outcome data); reporting bias (selective outcome reporting); and other sources of bias (Hooijmans et al., 2014).

3. Results

3.1. Search results

A total of 812 articles were identified across the four databases explored. Using the duplicate detection tool available on the Rayyan platform (https://new.rayyan.ai/), 456 duplicate articles were assessed and excluded manually. After reading the title and abstract, 342 articles were excluded. A full reading was carried out on 14 articles, with 2 being excluded. In the end, 12 articles were included in the review. Fig. 1 shows the flowchart detailing the selection stages.

3.2. Assessment of Quality of studies

In the risk of bias analysis, seven studies presented a high risk for sequence generation and allocation concealment by not describing the methods used (Andrews et al., 2009; Bayliss et al., 2016a,b; Liu et al., 2022; Minalyan et al., 2019; Rees et al., 2023; Wang et al., 2020), while the other five studies were classified as low risk of bias (He et al., 2021; Jiang et al., 2008; Jiao et al., 2021; Karasawa et al., 2014; Moon et al., 2009). All studies presented a low risk of bias for baseline

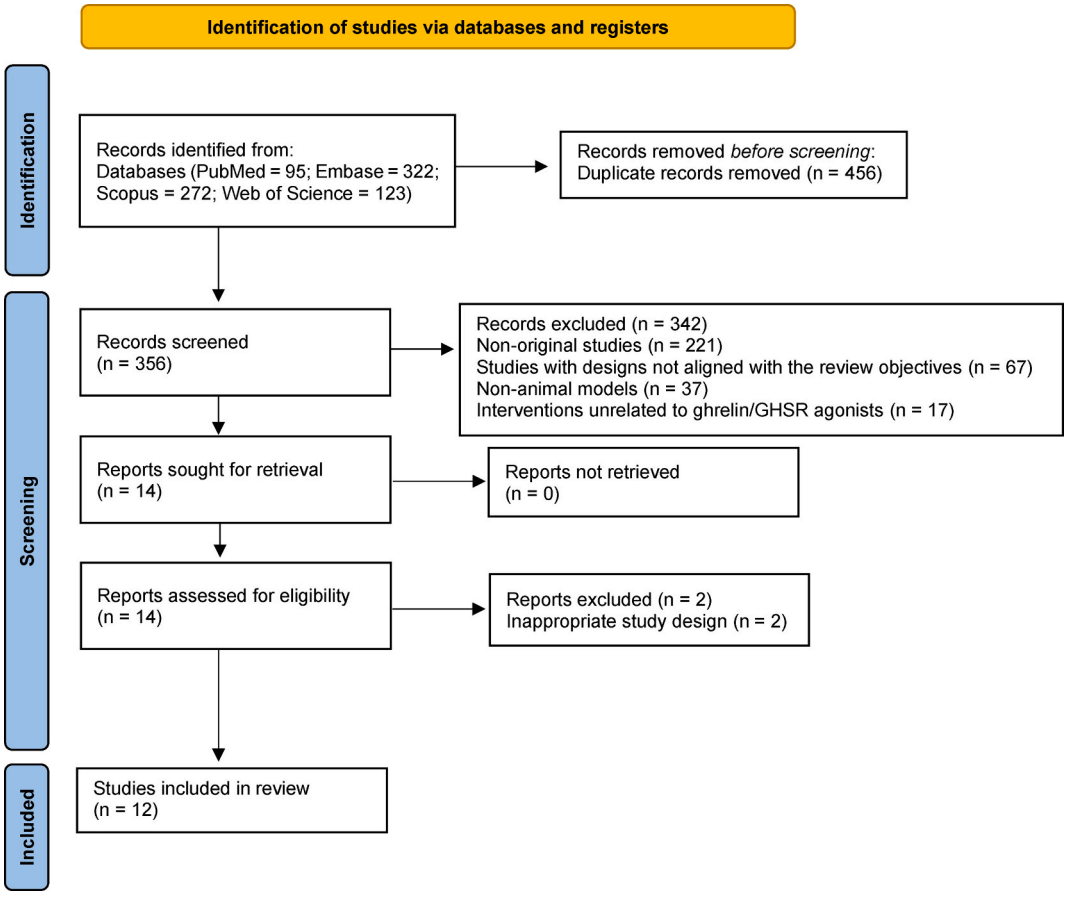

Fig. 1.

characteristics, but an unclear risk regarding random housing during the experiments. Only one study reported double blinding (He et al., 2021), while the other studies presented a high risk of bias for not indicating blinding of caregivers and/or investigators regarding the intervention each animal received (Andrews et al., 2009; Bayliss et al., 2016a,b; Jiang et al., 2008; Jiao et al., 2021; Karasawa et al., 2014; Liu et al., 2022; Minalyan et al., 2019; Moon et al., 2009; Rees et al., 2023; Wang et al., 2020). Five studies presented a low risk of bias for random selection of animals for outcome assessment (He et al., 2021; Jiao et al., 2021; Liu et al., 2022; Moon et al., 2009; Wang et al., 2020), while the other seven studies presented unclear risk (Andrews et al., 2009; Bayliss et al., 2016a,b; Jiang et al., 2008; Karasawa et al., 2014; Minalyan et al., 2019; Rees et al., 2023). Six studies reported outcome assessor blinding (Andrews et al., 2009; He et al., 2021; Jiang et al., 2008; Jiao et al., 2021; Minalyan et al., 2019; Rees et al., 2023), while the other six presented a high risk of bias (Andrews et al., 2009; Bayliss et al., 2016a, b; Karasawa et al., 2014; Minalyan et al., 2019; Moon et al., 2009; Rees et al., 2023). Seven studies did not provide adequate information on incomplete data and were classified as having a high risk of bias (Andrews et al., 2009; Bayliss et al., 2016a,b; Jiang et al., 2008; Karasawa et al., 2014; Minalyan et al., 2019; Rees et al., 2023). The other five studies were classified as low risk of bias in this domain (He et al., 2021; Jiao et al., 2021; Liu et al., 2022; Moon et al., 2009; Wang et al., 2020). All studies were classified as low risk of bias for selective reporting of results and other sources of bias (Figs. 2 and 3).

3.3. Methodological characteristics

Table 1 presents the characteristics of the included studies. Six of the twelve included studies were conducted using an MPTP-induced PD model (20–40 mg/kg, IP) in male C57BL/6 mice (Andrews et al., 2009; Bayliss et al., 2016a,b; Jiang et al., 2008; Moon et al., 2009; Wang et al., 2020). Four studies used a 6-OHDA-induced PD model (9–15 μg/3 μl) in male Sprague-Dawley rats (He et al., 2021; Karasawa et al., 2014; Minalyan et al., 2019; Rees et al., 2023), three of which were induced by injection into the medial forebrain bundle (MFB) (Karasawa et al., 2014; Minalyan et al., 2019; Rees et al., 2023) and one by the intracerebroventricular route (ICV) (He et al., 2021). Two studies were conducted with A53T mice (Jiao et al., 2021; Liu et al., 2022). Except for the two studies that started with 4-week-old A53T mice (Jiao et al., 2021; Liu et al., 2022), all other studies started with adult animals, some of which explicitly reported ages ranging from 8 to 11 weeks (Bayliss et al., 2016a,b; Jiang et al., 2008; Moon et al., 2009; Wang et al., 2020). Ghrelin intervention was performed in ten studies. Two studies performed ICV, with doses ranging from 50 to 400 ng/animal, with a single injection or daily injections for up to 14 consecutive days (He et al., 2021; Jiang et al., 2008). Four studies used exclusively the intraperitoneal (IP) route, with doses ranging from 20 to 160 μg/kg, and up to 1 mg/kg (Bayliss et al., 2016a,b; Moon et al., 2009; Wang et al., 2020), with only one study testing both acylated and des-acyled forms (Bayliss et al., 2016a,b). The duration of treatment ranged from multiple

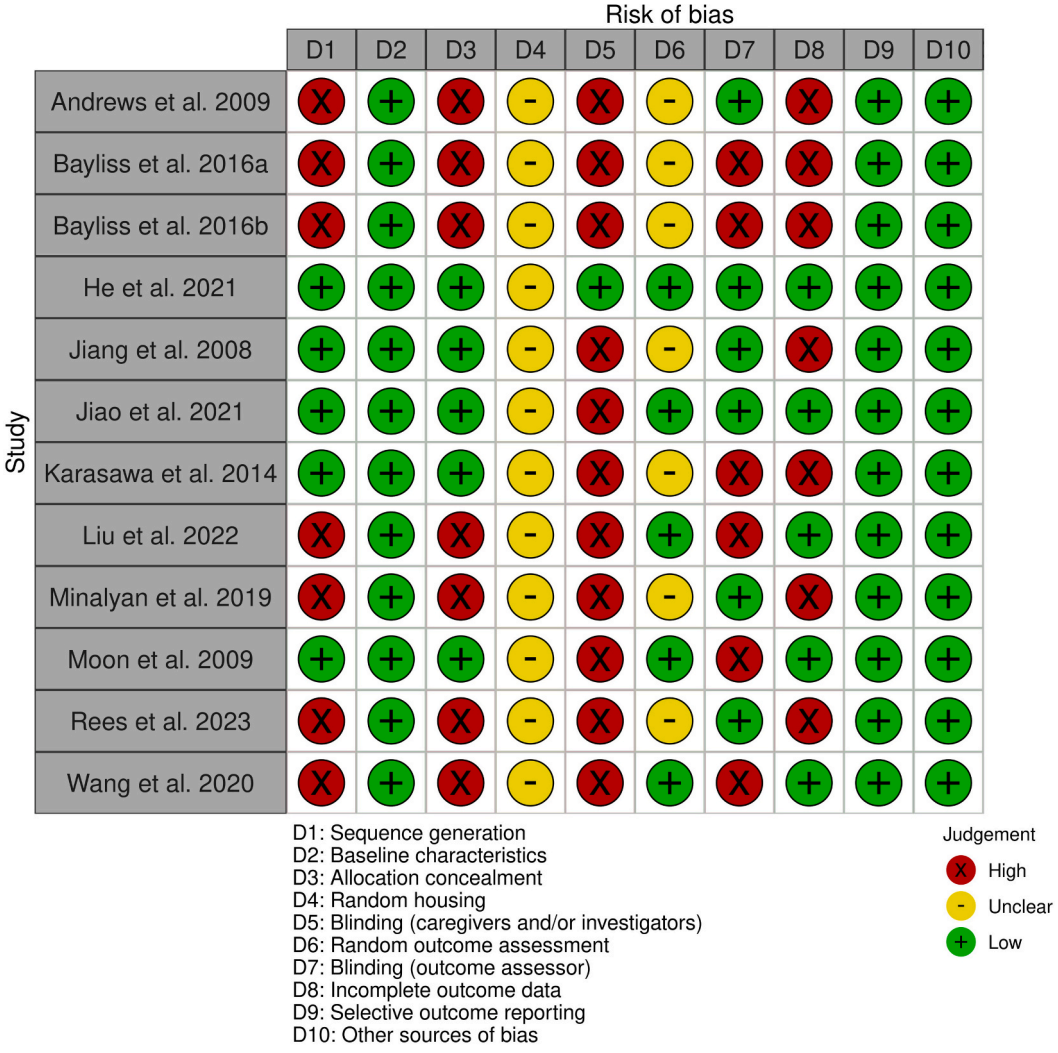

Fig. 2.

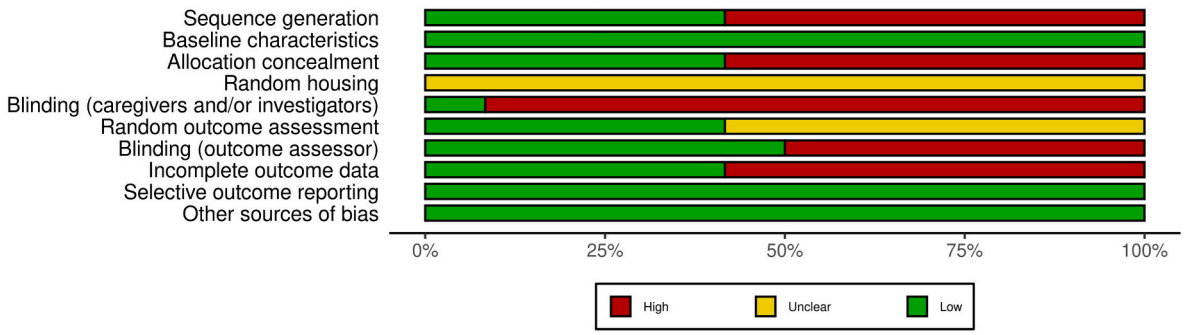

Fig. 3.

injections on a single day to daily injections for up to 14 consecutive days. Three studies performed the intervention via subcutaneous mini-osmotic pumps with doses of 80 μg/24 μl/day for seven days or at a physiological dose for 4 to 8 weeks (Jiao et al., 2021; Liu et al., 2022; Rees et al., 2023). One study used both IP (10 nmol/day) and mini-osmotic pumps (10 nmol/day), for 7 to 14 days depending on the treatment protocol (Andrews et al., 2009). Two studies performed the intervention with HM01, a GHSR-1a receptor agonist, which was administered via gavage at doses of 1, 3, or 10 mg/kg, with a single or daily injection for up to 12 consecutive days (Karasawa et al., 2014; Minalyan et al., 2019).

3.4. Main results of exogenous ghrelin administration

Table 2 presents the detailed results of the studies included. The two ICV studies demonstrated robust neuroprotective effects of ghrelin, including preservation of dopaminergic neurons in the SNpc, restoration of striatal DA and its metabolites, and attenuation of pro-apoptotic signaling in the SN (He et al., 2021; Jiang et al., 2008).

Regarding the four IP studies, consistent dopaminergic neuroprotective effects were observed, including increased TH-positive neurons in the SNpc, TH-positive fibers and dopamine levels in the striatum (Moon et al., 2009; Wang et al., 2020). Evidence from knockout models further indicated that these effects were form-dependent, with acylated ghrelin exerting robust neuroprotective and anti-inflammatory actions, while des-acylated ghrelin did not cause significant effects on the parameters, except for the elevation of corticosterone in plasma (Bayliss et al., 2016a,b).

Studies employing continuous ghrelin delivery via osmotic minipumps demonstrated consistent central and peripheral effects. Central effects included increased striatal dopamine, restoration of TH-positive neurons and TH protein levels in the SN, as well as reduced inflammation and increased antioxidant and antiapoptotic markers, which were accompanied by functional motor improvement (Jiao et al., 2021; Rees et al., 2023). Peripheral effects included reduced wet fecal weight and increased dry weight and frequency of bowel movements (Liu et al., 2022).

The study conducted by Andrews et al. (2009) performed the ghrelin intervention using two methods, via IP (10 nmol/day) and via osmotic minipumps (10 nmol/day) (Andrews et al., 2009). The administration of ghrelin via osmotic minipumps did not cause significant changes. Administration by IP, however, increased the number of TH-positive cells in the SNpc and elevated DA and DOPAC levels in the striatum, although it did not significantly alter the DOPAC/DA ratio (Andrews et al., 2009).

3.5. Main results of HM01 administration

Table 2 presents the detailed results of the studies included. Two studies performed intervention with HM01 via gavage. In the first study, treatment with HM01 increased fecal elimination and fecal water content. In addition, ghrelin increased the number of Fos-ir neurons in the arcuate nucleus, area postrema, and nucleus of the solitary tract (Karasawa et al., 2014). In the second study, HM01 caused an increase in body weight, fat mass, fecal weight in 24 h, fecal water content, water intake, and food intake (Minalyan et al., 2019).

4. Discussion

The aim of this review was to evaluate the effects of ghrelin or GHSR agonist intervention in experimental models of PD. Overall, the results obtained from the various models support the hypothesis that both preventive and therapeutic treatments could be beneficial for PD. In the MPTP model, intervention with ghrelin was able to reduce dopaminergic neurodegeneration and improve motor function. Ghrelin intervention in a 6-OHDA-induced PD model or in an A53-T transgenic model, in addition to dopaminergic neuroprotection and improved motor function, also had positive impacts on metabolic and gastrointestinal functions, expanding its relevance to non-motor consequences of PD.

4.1. Parkinson's disease models

Different PD models were used in the studies, each with distinct advantages and limitations in relation to the different aspects of PD that reproduce. MPTP was used by most studies. When metabolized in the brain, this toxin forms 1-methyl-4-phenyl-2,3-dihydropyridium (MPDP +) and subsequently 1-methyl-4-phenylpyridinium (MPP +) (Chiba et al., 1984). MPP + is absorbed by dopaminergic neurons via dopamine transporters (DAT), inhibiting mitochondrial complex I, causing oxidative stress and eventually cell death, generating a motor phenotype similar to that of PD in humans (Martinez and Greenamyre, 2012; Przedborski and Vila, 2003). This model does not, however, reproduce the alpha-synuclein (αS) aggregation pathology typical of Lewy bodies (Meredith and Rademacher, 2011). In the second most used model, PD was induced by 6-OHDA, an endogenous molecule found in trace amounts in the human brain and which, similar to MPTP, does not reproduce αS pathology (Blandini et al., 2008; Jellinger et al., 1995). Due to its inability to cross the blood–brain barrier, it must be administered by stereotactic injection or direct infusion into the brain (Blandini et al., 2008). Thus, its application can cause nigrostriatal lesions, also via mitochondrial deficits, with different degrees and profiles depending on the location of the injection (Blandini et al., 2008). In addition to the motor deficits caused by these models, a wide range of non-motor symptoms such as anosmia, pain, sleep disorders, cognitive deficits, depression, anxiety, psychosis, and gastrointestinal, cardiovascular, and urinary dysfunctions are found (Lama et al., 2021). However, it has been reported that the main weakness of these models is their inability to reproduce a slow progression model (Lama et al., 2021).

Lastly, the A53T model was used in two studies. Unlike the MPTP and 6-OHDA models, A53T is a transgenic mouse model that promotes

Table 1
Characteristics of the included studies.

Authors	Experimental groups	Sex	Age	Dosis	Duration
Jiang et al. 2008	Saline MPTPGhrelin pretreated	Male C57BL/6 mice	10 weeks	Saline = ICV MPTP = 30 mg/kg (IP) Ghrelin pretreated = 50, 100, 200, or 400 ng/mouse (ICV) + MPTP	Saline = once per day for 8 consecutive days MPTP = once per day for 5 consecutive daysGhrelin pretreated = once per day for 8 consecutive days + MPTP in the last 5 days
Andrews et al. 2009	Saline MPTP Ghrelin MPTPGhrelin MPTP	Male C57/6 mice	Adult	Saline (IP) MPTP = 40 mg/kg (IP) Ghrelin MPTP = 10 nmol/day (osmotic minipumps) + MPTP Ghrelin MPTP = 10 nmol/day (IP) + MPTP	Saline = One dose after 7 days of ghrelin intervention (in place of MPTP) and/or osmotic minipumps for seven days (in place of ghrelin) MPTP = One dose after 7 days of ghrelin intervention Ghrelin MPTP = Osmotic minipumps for seven daysGhrelin MPTP = Daily injections of ghrelin for 7 d before and 7 d after MPTP injections
Moon et al. 2009	Saline MPTP Ghrelin + MPTPMPTP + Ghrelin	Male C57BL/6 mice	8 weeks	Saline (IP) MPTP = 20 mg/kg (IP) Ghrelin + MPTP = 20, 40, 80, or 160 μg/kg (IP) + MPTP MPTP + Ghrelin = MPTP + 80 μg/kg (IP)	Saline = four injections in a single day (2-h intervals) MPTP = four injections in a single day (2-h intervals) Ghrelin + MPTP = 2 h before the first MPTP injection and 30 min prior to each MPTP injection (total = five doses)MPTP + Ghrelin = two injections, the first 2 h after the last MPTP injection and the second 2 h later, and once daily for 6 additional days (total = eight doses)
Karasawa et al. 2014	Vehicle 6-OHDA6-OHDA + HM01	Male Sprague-Dawley rats	Adult	Vehicle = Unilateral microinjection of 3 μL saline (0.2% ascorbic acid) into the MFB 6-OHDA = Unilateral microinjection of 6-OHDA (12 μg in 3 μL saline with 0.2% ascorbic acid) into the MFB6-OHDA + HM01 = 6-OHDA + 1, 3, or 10 mg/kg orally administered via gavage	Vehicle = single session, followed by 3 weeks of recovery 6-OHDA = single session, followed by 4 weeks of recovery 6-OHDA + HM01 = 6-OHDA + single dose (fecal output and water content, gastric emptying, and c-Fos expression) or once per day for 7 consecutive days (food/water intake, body weight, and gastric emptying) starting from 4 weeks after microinjection
Bayliss et al. 2016a	Ghrelin KO Saline + Saline MPTP + Saline MPTP + Acyl ghrelinMPTP + Des-acyl ghrelin	Male C57/BL6	8–10 weeks	Saline (IP) MPTP = 30 mg/kg (IP) Acylated ghrelin = 1 mg/kg (IP) Des-acyl ghrelin = 1 mg/kg (IP)	Saline = administered once daily for 14 consecutive days (in place of ghrelin treatment) and/or once daily for 2 consecutive days (in place of MPTP) MPTP = Once per day for 2 consecutive days, with or without prior 7-day ghrelin treatment Acylated ghrelin = once per day for 14 consecutive daysDes-acyl ghrelin = once per day for 14 consecutive days
Bayliss et al. 2016b	AMPK WT/KO WT + Saline KO + Saline WT + MPTP KO + MPTP WT + MPTP + GhrelinKO + MPTP + Ghrelin	Male C57/BL6J	8–10 weeks	Saline (IP) MPTP = 30 mg/kg (IP) Acylated ghrelin = 1 mg/kg (IP)	Saline = administered once daily for 14 consecutive days (in place of ghrelin treatment) and/or once daily for 2 consecutive days (in place of MPTP) MPTP = Once per day for 2 consecutive days, with or without prior 7-day ghrelin treatmentAcylated ghrelin = once per day for 14 consecutive days
Minalyan et al. 2019	Vehicle 6-OHDA6-OHDA + HM01	Male Sprague-Dawley rats	Adult	Vehicle = unilateral microinjection of 3 μL saline (0.2% ascorbic acid) into the MFB 6-OHDA = unilateral microinjection of 6-OHDA (12 μg in 3 μL saline with 0.2% ascorbic acid) into the MFB6-OHDA + HM01 = 6-OHDA + 3 mg/kg orally administered via gavage	Vehicle = single session, followed by 3 weeks of recovery 6-OHDA = single session, followed by 3 weeks of recovery6-OHDA + HM01 = 6-OHDA + once per day for 10 to 12 consecutive days starting from 4 weeks after microinjection
Wang et al. 2020	Control MPTP Ghrelin + MPTP	Male C57BL/6 mice	9–11 weeks	Control = saline (IP) MPTP = 30 mg/kg (IP) Ghrelin + MPTP = 40, 60, or 80 μg/kg (IP)	Control = saline once per day for a total of six injections MPTP = once per day for 5 consecutive daysGhrelin + MPTP = 2h before the first MPTP injection and 30 min before each MPTP injection for a total of six injections
He et al. 2021	Control 6-OHDAGhrelin + 6-OHDA	Male Sprague-Dawley rats	Adult	Control = saline 0.02% ascorbic acid in 0.9% saline (ICV) 6-OHDA = 15 μg in 3 μl of saline with 0.02% ascorbic acid (ICV) Ghrelin + 6-OHDA = 100, 200, and 400 ng/mouse (ICV)	Control = one single session 6-OHDA = single session Ghrelin + 6-OHDA = 6-OHDA + single dose (autophagy-lysosome pathway) administered ICV 30 min before 6-OHDA injection, or once per day for 14 consecutive days (behavioral changes and the survival dopaminergic neurons) starting from the day of 6-OHDA microinjection
Jiao et al. 2021	P-WT P-A53TG-A53T	A53T mice	4 weeks	Nonsense peptide = subcutaneously in saline via Alzet mini–osmotic pumps at a low dose (dose not specified) Ghrelin = subcutaneously in saline via Alzet mini–osmotic pumps at a low dose (dose not specified)	Nonsense peptide or Ghrelin = starting at the age of 1 month, lasting for 4 or 8 weeks
Liu et al. 2022	P-A53TG-A53T	A53T mice	4 weeks	Nonsense peptide = subcutaneously in saline via Alzet mini–osmotic pumps Ghrelin = subcutaneously in saline via Alzet mini–osmotic pumps at a low dose (contained acylated ghrelin as physiological level)	Nonsense peptide or Ghrelin = starting at the age of 1 month, lasting for 8 weeks; harvested at the age of 3 or 6 months (3 m or 6 m)

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Table 1 (*continued*)

Authors	Experimental groups	Sex	Age	Dosis	Duration
Rees et al. 2023	Sham LesionAcyl-ghrelin/ lesion group	Male Sprague-Dawley rats	Adult	Sham vehicle = Subcutaneous dummy Alzet osmotic minipumps + MFB injection (0.2 mg/ml ascorbic acid in 0.9% sterile saline) Lesion = Subcutaneous osmotic minipumps primed to deliver sterile isotonic saline (80 μg/24 μl/day) + MFB injection (6-OHDA 3 μg/μl: 9 μg)Acyl-ghrelin/lesion group = Subcutaneous osmotic minipumps primed to deliver acyl-ghrelin (80 μg/ 24 μl/day) + MFB injection (6-OHDA 3 μg/μl: 9 μg)	Sham vehicle = A subcutaneous dummy osmotic minipump was implanted and remained in place for 7 consecutive days. After this period, a single unilateral injection of ascorbic acid in saline (vehicle) was administered into the MFB Lesion = A subcutaneous osmotic minipump was implanted to deliver sterile isotonic saline continuously for 7 days. After this period, a single unilateral injection of 6–hydroxydopamine (6–OHDA) was administered into the MFB Acyl-ghrelin/lesion group = A subcutaneous osmotic minipump was implanted to deliver acyl–ghrelin continuously for 7 days, followed by a single unilateral injection of 6–hydroxydopamine (6–OHDA) into the MFB

overexpression of the mutant A53T form of αS, simulating a progressive model of PD (Jiao et al., 2021; Rothman et al., 2013). This is important as ghrelin deficiency is observed in pre-motor stages, which has been linked to the loss of choline acetyltransferase (ChAT)-positive neurons in the dorsal motor nucleus of the vagus nerve (DMV) (Liu et al., 2022). This model causes various motor and autonomic changes, as well as inflammatory changes, but usually does not present cognitive deficits, depression, or anxiety (Lama et al., 2021). Given the limited number of studies included in this review that use progressive models, new studies could explore these models to investigate more completely how ghrelin intervention may influence PD progression. Considering that each PD model offers distinct opportunities to study specific aspects of the disease with different limitations, the development of combined models should be encouraged to capture multiple pathological features simultaneously. This approach may improve the translational relevance of preclinical results, allowing for a more accurate assessment of the effects of ghrelin.

4.2. Dependence on GHSR-1a and acylated form of ghrelin

Since the motor impairments of PD mainly result from the progressive degeneration of dopaminergic neurons in the SNpc, many studies have evaluated the effects of ghrelin on this parameter, with different mechanisms proposed. First, it is important to note that the effects of ghrelin were completely GHSR-1a-dependent, given that the use of D-Lys3-GHRP-6, a GHSR-1a receptor inhibitor used in many of the included studies, completely blocked the protective effects of ghrelin (Jiang et al., 2008). Secondly, when comparing the two forms of ghrelin, acylated and des-acylated, only the acylated form provided benefits. Although *in vitro* studies have shown significant results using the des-acylated form, the lack of *in vivo* effects may be associated with increased corticosterone production triggered by this form of ghrelin (Bayliss et al., 2016a,b). Thus, the available evidence suggests that therapeutic strategies targeting ghrelin in PD should prioritize GHSR-1a activation and the stabilization of acylated ghrelin levels.

4.3. Mechanisms of neuroprotection

4.3.1. Regulation of apoptosis and endoplasmic reticulum stress

The first neuroprotection mechanism involves protection from apoptosis, including the regulation of Bcl-2 and Bax proteins in the mitochondrial pathway (Jiang et al., 2008) and the suppression of endoplasmic reticulum stress signals (ERS) (Wang et al., 2020). The Bcl-2 protein family regulates mitochondrial permeability and the cellular apoptotic pathway, with the balance between Bcl-2 (anti-apoptotic) and Bax (pro-apoptotic) being decisive for cell survival (Reed, 1997; Vila et al., 2001). MPTP, by reducing Bcl-2 expression and increasing Bax expression, generates an imbalance that leads to caspase-3-mediated apoptosis (Jiang et al., 2008). In turn, treatment with ghrelin reduced dopaminergic neuronal death and prevented MPTP-induced declines in DA levels by reducing caspase-3 activation through increasing Bcl-2 expression and reducing Bax expression (Jiang et al., 2008). Although without firsthand evidence, the authors also suggested that ghrelin may reduce the production of reactive oxygen species (ROS), especially hydroxyl radicals, by reducing iron accumulation in the SNpc (Jiang et al., 2008). In addition to caspase-3, reductions in caspase-12, which activates caspase-3 and is located in the endoplasmic reticulum, have also been reported (Wang et al., 2020). This reduction was also accompanied by changes in ERS regulators, including GRP78 (Lee, 2005), enhanced by MPTP and attenuated by ghrelin (Wang et al., 2020).

4.3.2. Mitochondrial function, neuronal activity, and oxidative stress

In addition to modulating the Bcl-2/Bax balance, regulating caspase-3, caspase-12, and ERS, ghrelin also electrically activates dopaminergic neurons in the SNpc, stimulates mitochondrial respiration dependent on uncoupling protein 2 (UCP-2), reduces microglial activation, and promotes autophagy regulation (Andrews et al., 2009; Moon et al., 2009; Wang et al., 2020). UCP-2, a mitochondrial anion transport protein, regulates both mitochondrial ATP production and ROS generation (Toda and Diano, 2014). While the acute effect of ghrelin on the electrical activity of neurons in the SNpc causes an increase in dopamine availability in the dorsal striatum, increased respiration and mitochondrial proliferation via UCP-2 confers an energetic status that makes neurons more resistant to cell death (Andrews et al., 2009). Interestingly, these effects were dependent on metabolic status, indicating that the presence of glucose inhibited the pathway involving AMPK, carnitine palmitoyltransferase I (CPT1), and UCP2 (AMPK-CPT1-UCP2 pathway), blocking the neuroprotection conferred by ghrelin (Andrews et al., 2009). These findings also reinforce the role of AMPK, since it has also been reported as an actor mediating the neuroprotective effect conferred by ghrelin in a context of caloric restriction (Bayliss et al., 2016a,b). Within the context of oxidative stress, a study also reported increased SOD1 activity following ghrelin intervention (Jiao et al., 2021).

4.3.3. Microglial activation and neuroinflammation

Regarding microglial activation and consequent neurodegeneration, different molecules are important, including MMP-3, released from stressed dopaminergic neurons (Kim et al., 2005). In this context, ghrelin intervention was able to attenuate the expression of pro-MMP-3 and MMP-3 in the SNpc and consequently microglial activation in the SNpc and striatum, in addition to suppressing the expression of TNF-α, IL-1β, and iNOS in the midbrain (Moon et al., 2009). A recent review indicated that PD is associated with an imbalance in central and peripheral cytokine levels, resulting in a chronic low-grade pro-inflammatory phenotype (Dzamko, 2023), which corroborates the relevance of the results obtained with ghrelin intervention.

Table 2
Main results.

Outcomes	Study	Experimental group	Main findings	Comparison
Overall dopaminergic system integrity	Jiang et al. 2008	MPTP	↓ TH-ir neurons in SNpc	Survival rate: 67% vs control
		Ghrelin 50 or 100 ng	↔ TH-ir neurons in SNpc	—
		Ghrelin 200 ng	Preserved TH-ir neurons in SNpc ★	vs MPTP; $p < 0.05$
		Ghrelin 400 ng	Preserved TH-ir neurons in SNpc ★	vs MPTP; $p < 0.05$
	Andrews et al. 2009	MPTP	↓ TH cell number in the SNpc	vs saline; $p < 0.05$
		Ghrelin (osmotic minipumps)	↔ TH cell number in the SNpc	—
		Ghrelin (IP)	↑ TH cell number in the SNpc ★	vs MPTP; $p < 0.05$
	Moon et al. 2009	MPTP	↓ TH-positive neurons in SNpc	vs saline; $p < 0.05$
		Ghrelin MPTP (20 μg/kg)	↔ TH-positive neurons in SNpc	—
		Ghrelin MPTP (40, 80, or 160 μg/kg)	↑ TH-positive neurons in SNpc ★	vs MPTP; $p < 0.05$
		MPTP Ghrelin (80 μg/kg)	↑ TH-positive neurons in SNpc ★	vs MPTP; $p < 0.05$
		MPTP	↓ striatal TH-positive fibers	vs saline; $p < 0.05$
		Ghrelin MPTP (20 μg/kg)	↔ striatal TH-positive fibers	—
		Ghrelin MPTP (40, 80, or 160 μg/kg)	↑ striatal TH-positive fibers ★	vs MPTP; $p < 0.05$
		MPTP Ghrelin (80 μg/kg)	↑ striatal TH-positive fibers ★	vs MPTP; $p < 0.05$
		MPTP	↓ striatal TH protein levels	vs saline; $p < 0.05$
		Ghrelin MPTP (80 μg/kg)	Preserved striatal TH protein reduction ★	vs MPTP; $p < 0.05$
	Bayliss et al. 2016a	MPTP	↓ number and size of TH neurons in the SN	
		Acylated ghrelin	↓ reduction in the number and size of TH neurons in the SN ★	vs Saline/Saline; $p < 0.05$
		Des-acylated ghrelin	↔ number and size of TH neurons in the SN	vs Saline/MPTP; $p < 0.05$
		MPTP	↓ TH levels in the SN and striatum	vs Saline/Saline; $p < 0.05$
		Acylated ghrelin	↓ reduction in the TH levels in the SN and striatum ★	vs Saline/MPTP; $p < 0.05$
		Des-acylated ghrelin	↔ TH levels in the SN and striatum	—
	Bayliss et al. 2016b	MPTP	↓ number of TH neurons in the SNpc	vs WT/KO Saline; $p < 0.05$
		Ghrelin	↑ number of TH neurons in the SNpc ★	vs WT Saline/MPTP; $p < 0.05$
		MPTP	↔ TH cell volume in the SNpc	—
		Ghrelin	↔ TH cell volume in the SNpc	—
		MPTP	↓ TH protein expression in the SN and striatum	vs WT/KO Saline; $p < 0.05$
		Ghrelin	↑ TH protein expression in the SN and striatum ★	vs WT Saline/MPTP; $p < 0.05$
	Wang et al. 2020	MPTP	↓ number of TH-positive neurons in the SNpc	vs control; $p < 0.001$
		MPTP Ghrelin (40 μg/kg)	↔ number of TH-positive neurons in the SNpc	—
		MPTP Ghrelin (60 μg/kg)	↑ number of TH-positive neurons in the SNpc ★	vs MPTP; $p < 0.01$
		MPTP Ghrelin (80 μg/kg)	↑ number of TH-positive neurons in the SNpc ★	vs MPTP; $p < 0.001$
		MPTP	↓ expression of TH in the SNpc and striatum	vs control; $p < 0.01$
		MPTP Ghrelin (80 μg/kg)	↑ expression of TH in the SNpc and striatum ★	vs MPTP; $p < 0.05$
		MPTP	↓ density of TH fibers in the SNpc	vs control; $p < 0.001$
		MPTP Ghrelin (40 μg/kg)	↔ density of TH fibers in the SNpc	—
		MPTP Ghrelin (60 μg/kg)	↑ density of TH fibers in the SNpc ★	vs MPTP; $p < 0.05$
		MPTP Ghrelin (80 μg/kg)	↑ density of TH fibers in the SNpc ★	vs MPTP; $p < 0.001$
	He et al. 2021	6-OHDA	↓ TH expression in the SN weeks after 6-OHDA intoxication	vs control; $p < 0.01$
		Ghrelin (100 and 200 ng)	↑ TH expression in the SN weeks after 6-OHDA intoxication ★	vs 6-OHDA; $p < 0.01$
		Ghrelin (400 ng)	↑ TH expression in the SN, but with lower magnitude compared to 100 and 200 ng in the SN weeks after 6-OHDA intoxication	vs 6-OHDA; $p < 0.01$
	Jiao et al. 2021	P-A53T (4 weeks)	↓ number of TH-positive cells and protein levels in the SN at 3 months of age	vs P-WT; $p < 0.01$ and < 0.05
		P-A53T (8 weeks)	↓ number of TH-positive cells and protein levels in the SN at 3 months of age	vs P-WT; $p < 0.05$
		P-A53T (8 weeks)	↓ number of TH-positive cells and protein levels in the SN at 6 months of age	vs P-WT; $p < 0.01$ and < 0.05
		G-A53T (4 weeks)	↔ number of TH-positive cells and protein levels in the SN at 3 months of age	—

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Table 2 (*continued*)

Outcomes	Study	Experimental group	Main findings	Comparison
		G-A53T (8 weeks)	↑ number of TH-positive cells and protein levels in the SN at 3 months of age ★	vs P-A53T; $p < 0.05$
		G-A53T (8 weeks)	↑ number of TH-positive cells and protein levels in the SN at 6 months of age ★	vs P-A53T; $p < 0.01$ and < 0.05
	Rees et al. 2023	6-OHDA	↓ number of TH-positive cells in the ipsilateral SNpc	vs Sham; $p < 0.0001$
		Acyl-ghrelin	↑ number of TH-positive cells in the ipsilateral SNpc ★	vs 6-OHDA; $p < 0.01$
Overall dopaminergic neurochemistry	Jiang et al. 2008	MPTP	↓ DA, DOPAC, and HVA levels in the striatum	72% vs control
		Ghrelin 50 ng	↔ DA, DOPAC, and HVA levels in the striatum	—
		Ghrelin 100 ng	↑ DA levels in the striatum	vs MPTP; $p < 0.01$
		Ghrelin 200 ng	↑ DA, DOPAC, and HVA levels in the striatum ★	vs MPTP; $p < 0.01$
		Ghrelin 400 ng	↑ DA, DOPAC, and HVA levels in the striatum ★	vs MPTP; $p < 0.01$
	Andrews et al. 2009	MPTP	↓ DA, DOPAC, and increased DOPAC/DA ratio in striatum	vs saline; $p < 0.05$
		Ghrelin (osmotic minipumps)	↔ DA, DOPAC, and DOPAC/DA ratio in striatum	—
		Ghrelin (IP)	↑ DA and DOPAC, but no effect on DOPAC/DA ration in striatum ★	vs MPTP; $p < 0.05$
	Moon et al. 2009	MPTP	↓ striatal dopamine levels	vs saline; $p < 0.05$
		Ghrelin MPTP (20 μg/kg)	↔ striatal dopamine levels	—
		Ghrelin MPTP (40, 80, or 160 μg/kg)	↑ striatal dopamine levels ★	vs MPTP; $p < 0.05$
	Bayliss et al. 2016a	MPTP	↓ DOPAC and dopamine levels in the SN	vs Saline/Saline; $p < 0.05$
		Acylated ghrelin	Prevented DOPAC:DA ratio increase in the SN ★	vs Saline/MPTP; $p < 0.05$
		Des-acylated ghrelin	↔ DOPAC and dopamine levels, and DOPAC:DA ratio in the SN	—
	Bayliss et al. 2016b	MPTP	↓ DA but not DOPAC levels in the striatum	vs WT Saline; $p < 0.05$
			↓ DA and DOPAC levels in the striatum	vs KO Saline; $p < 0.05$
		Ghrelin	↑ DA levels in the striatum ★	vs WT Saline/MPTP; $p < 0.05$
	Jiao et al. 2021	P-A53T (4 weeks)	↓ DA content in the striatum at 3 months of age	vs P-WT; $p < 0.05$
		P-A53T (8 weeks)	↓ DA content in the striatum at 3 and 6 months of age	vs P-WT; $p < 0.001$
		G-A53T (4 weeks)	↑ DA content in the striatum at 3 months of age	vs P-A53T; $p < 0.01$
		G-A53T (8 weeks)	↑ DA content in the striatum at 3 and 6 months of age ★	vs P-A53T; $p < 0.0001$ and < 0.01
Overall apoptosis assessment	Jiang et al. 2008	MPTP	↓ Bcl-2 and increased Bax expression. in the SN	vs control
		Ghrelin 100, 200, 400 ng	↓ Bcl-2 decrease and Bax increase in the SN ★	vs MPTP; $p < 0.01$
		Ghrelin 50 ng	↓ Bax increase in the SN	vs MPTP; $p < 0.01$
		MPTP	↑ caspase-3 activation in the SN	349% vs control
		Ghrelin 50 or 100 ng	↔ caspase-3 activation in the SN	—
		Ghrelin 200 ng	↓ caspase-3 activation in the SN ★	vs MPTP; $p < 0.01$
		Ghrelin 400 ng	↓ caspase-3 activation in the SN ★	vs MPTP; $p < 0.01$
		MPTP	↑ expression of GRP78 in the SNpc, striatum, and dopaminergic neurons	vs control; $p < 0.001$
			↑ expression of p-IRE1α, XBP1s, CHOP, p-ASK1, and p-JNK in the SNpc	vs control; $p < 0.01$, < 0.01, < 0.05, < 0.05, and < 0.01
			↑ expression of p-IRE1α, XBP1s, CHOP, p-ASK1, and p-JNK in the striatum	vs control; $p < 0.05$, < 0.05, < 0.001, < 0.01, and < 0.05
			↑ expression of CHOP in dopaminergic neurons	vs control; $p < 0.001$
			↑ activation of cleaved caspase-12 and Cleaved caspase-3 in the SNpc	vs control; $p < 0.05$ and < 0.01
			↑ activation of cleaved caspase-12 and Cleaved caspase-3 in the striatum	vs control; $p < 0.001$ and < 0.05
	Wang et al. 2020		↑ activation of cleaved caspase-12 and Cleaved caspase-3 in dopaminergic neurons	vs control; $p < 0.001$
			↓ ratio of Bcl-2/Bax in the SNpc and striatum	vs control; $p < 0.01$ and < 0.001
		MPTP Ghrelin (80 μg/kg)	↓ expression of GRP78 in the SNpc, striatum, and dopaminergic neurons ★	vs MPTP; $p < 0.05$, < 0.001, and < 0.05
			↓ expression of p-IRE1α, XBP1s, CHOP, p-ASK1, and p-JNK in the SNpc ★	vs MPTP; $p < 0.05$, < 0.01, < 0.05, < 0.05, and < 0.05
			↓ expression of p-IRE1α, XBP1s, CHOP, p-ASK1, and p-JNK in the striatum ★	vs MPTP; $p < 0.05$, < 0.05, < 0.05, < 0.01, and < 0.05
			↓ expression of CHOP in dopaminergic neurons ★	vs MPTP; $p < 0.001$
			↓ activation of cleaved caspase-12 and Cleaved caspase-3 in the SNpc ★	vs MPTP; $p < 0.05$ and 0.01

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Table 2 (*continued*)

Outcomes	Study	Experimental group	Main findings	Comparison
			↓ activation of cleaved caspase-12 and Cleaved caspase-3 in the striatum ★	vs MPTP; $p < 0.05$
			↓ activation of cleaved caspase-12 and Cleaved caspase-3 in dopaminergic neurons ★	vs MPTP; $p < 0.05$
			↑ ratio of Bcl-2/Bax in the SNpc and striatum ★	vs MPTP; $p < 0.05$
	He et al. 2021	6-OHDA	↑ bax/bcl-2 ratio and expression of cleaved caspase 3 in SN 1 day after 6-OHDA intoxication	vs control; $p < 0.01$ and < 0.05
		Ghrelin (100 ng)	↓ bax/bcl-2 ratio and expression of cleaved caspase 3 in SN 1 day after 6-OHDA intoxication ★	vs 6-OHDA; $p < 0.01$
		6-OHDA	↑ number of TH and cleaved caspase three double positive cells in SN 1 day after 6-OHDA intoxication	vs control; $p < 0.01$
		Ghrelin (100 ng)	↓ number of TH and cleaved caspase three double positive cells in SN 1 day after 6-OHDA intoxication ★	vs 6-OHDA; $p < 0.01$
	Jiao et al. 2021	P-A53T (4 weeks)	↔ ratio Bcl-2/Bax in the SN at 3 months of age	—
		P-A53T (8 weeks)	↓ ratio of Bcl-2/Bax in the SN at 6 but not 3 months of age	vs P-WT; $p < 0.01$
		G-A53T (4 weeks)	↔ ratio Bcl-2/Bax in the SN at 3 months of age	—
		G-A53T (8 weeks)	↑ ratio of Bcl-2/Bax in the SN at 6 but not 3 months of age ★	vs P-WT; $p < 0.01$
Overall glial response	Moon et al. 2009	MPTP	↑ microglial activation in SNpc and striatum	vs saline; $p < 0.05$
		MPTP Ghrelin (80 μg/kg)	↓ microglial activation in SNpc and striatum ★	vs MPTP; $p < 0.05$
		MPTP	↑ TNF-α, IL-1β, and iNOS expression in the midbrain	vs saline; $p < 0.05$
		MPTP Ghrelin (80 μg/kg)	↓ TNF-α, IL-1β, and iNOS expression in the midbrain ★	vs MPTP; $p < 0.05$
	Bayliss et al. 2016a	MPTP	↑ microglia and astrocytes number in the SN	vs Saline/Saline; $p < 0.05$
		Acylated ghrelin	↓ microglial, but not astrocytes number, in the SN ★	vs Saline/MPTP; $p < 0.05$
		Des-acylated ghrelin	↔ microglia and astrocytes number in the SN	—
	Bayliss et al. 2016b	MPTP	↑ microglia and astrocytes number in the SNpc	vs WT/KO Saline; $p < 0.05$
		Ghrelin	↓ microglia and astrocytes number in the SNpc ★	vs WT Saline/MPTP; $p < 0.05$
	Jiao et al. 2021	P-A53T (4 weeks)	↑ number of microglia in the SN at 3 months of age	vs P-WT; $p < 0.01$
		P-A53T (8 weeks)	↑ number of microglia in the SN at 3 and 6 months of age	vs P-WT; $p < 0.05$
		G-A53T (4 weeks)	↔ number of microglia in the SN at 3 months of age	—
		G-A53T (8 weeks)	↓ number of microglia in the SN at 3 and 6 months of age ★	vs P-A53T; $p < 0.05$
		P-A53T (4 weeks)	↑ expression of IL-6 in the SN at 3 months of age	vs P-WT; $p < 0.05$
		P-A53T (8 weeks)	↑ expression of IL-6 in the SN at 3 and 6 months of age	vs P-WT; $p < 0.05$
		P-A53T (8 weeks)	↓ expression of IL-10 in the SN at 3 months of age	vs P-WT; $p < 0.05$
		P-A53T (8 weeks)	↔ expression of TNF-α in the SN at 3 and 6 months of age	—
		G-A53T (4 weeks)	↔ expression of IL-6 in the SN at 3 months of age	—
		G-A53T (8 weeks)	↓ expression of IL-6 in the SN at 3 and 6 months of age ★	vs P-A53T; $p < 0.05$
		G-A53T (8 weeks)	↔ expression of IL-10 in the SN at 3 and 6 months of age	—
		G-A53T (8 weeks)	↔ expression of TNF-α in the SN at 3 and 6 months of age	—
Overall cellular stress and survival pathways	Moon et al. 2009	MPTP	↑ nitrotyrosine-positive neurons in the SNpc	vs saline; $p < 0.05$
		Ghrelin MPTP (80 μg/kg)	↓ nitrotyrosine-positive neurons in the SNpc ★	vs MPTP; $p < 0.05$
		MPTP	↑ MMP-3 and pro-MMP-3 expression in SNpc	vs saline; $p < 0.05$
		MPTP Ghrelin (80 μg/kg)	↓ MMP-3 and pro-MMP-3 up-regulation in SNpc ★	vs MPTP; $p < 0.05$
	Bayliss et al. 2016b	MPTP	↑ pAMPK/AMPK expression in the striatum	vs WT Saline/MPTP; $p < 0.05$
		Ghrelin	↔ pAMPK/AMPK expression in the striatum	—
		MPTP	↑ pACC/ACC expression in the striatum	vs WT Saline/MPTP; $p < 0.05$
		Ghrelin	↔ pACC/ACC expression in the striatum	—
		MPTP	↔ LC3 II expression in the SN and striatum	—
		Ghrelin	↔ LC3 II expression in the SN and striatum	—
	Wang et al. 2020	MPTP	↓ LC3B-II and Beclin1 expression and ↑ p62 expression in the SNpc	vs control; $p < 0.01$
			↓ LC3B-II and Beclin1 expression and ↑ p62 expression in the striatum	vs control; $p < 0.001$ and < 0.01
			↓ LC3B-II and Beclin1 expression and ↑ p62 expression in dopaminergic neurons	vs control; $p < 0.001$
		MPTP Ghrelin (80 μg/kg)	↑ LC3B-II and Beclin1 expression and ↓ p62 expression in the SNpc and striatum ★	vs MPTP; $p < 0.05$
			↑ LC3B-II and Beclin1 expression and ↓ p62 expression in dopaminergic neurons ★	vs MPTP; $p < 0.001$, < 0.05, and 0.001
	He et al. 2021	6-OHDA	↑ percentage of TH and LC3 double positive cells in SN 1 day after 6-OHDA intoxication	vs control; $p < 0.01$

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Table 2 (*continued*)

Outcomes	Study	Experimental group	Main findings	Comparison
			↑ expression of Atg7 and LC3-II in SN 1 day after 6-OHDA intoxication	vs control; $p < 0.01$
			↓ expression of p62 in SN 1 day after 6-OHDA intoxication	vs control; $p < 0.05$
		Ghrelin (100 ng)	↑ percentage of TH and LC3 double positive cells in SN 1 day after 6-OHDA intoxication	vs control; $p < 0.01$
			↑ expression of Atg7 and LC3-II in SN 1 day after 6-OHDA intoxication	vs control and 6-OHDA; $p < 0.05$
			↓ expression of p62 in SN 1 day after 6-OHDA intoxication	vs control and 6-OHDA; $p < 0.01$
	Jiao et al. 2021	P-A53T (4 weeks)	↔ expression of SOD1 in the SN at 3 months of age	—
		P-A53T (8 weeks)	↓ expression of SOD1 in the SN at 6 but not 3 months of age	vs P-WT; $p < 0.0001$
		G-A53T (4 weeks)	↔ expression of SOD1 in the SN at 3 months of age	—
		G-A53T (8 weeks)	↑ expressoin of SOD1 in the SN at 6 but not 3 months of age ★	vs P-A53T; $p < 0.001$
Overall motor function	Moon et al. 2009	MPTP	↓ rota-rod latency to fall	vs saline; $p < 0.05$
		Ghrelin MPTP (20 μg/kg)	↔ rota-rod latency to fall	—
		Ghrelin MPTP (40, 80, or 160 μg/kg)	↑ rota-rod latency to fall ★	vs MPTP; $p < 0.05$
	Bayliss et al. 2016b	Ghrelin	↑ latency to fall ★	vs WT Saline/MPTP; $p < 0.05$
	Minalyan et al. 2019	6-OHDA	↓ adjusted steps (forelimb akinesia)	vs vehicle; $p < 0.05$
		HM01	↔ adjusted steps	—
		6-OHDA	↑ rotations	vs vehicle; $p < 0.05$
		HM01	↔ rotations	—
	Wang et al. 2020	MPTP	↓ latency to fall	vs control; $p < 0.001$
		MPTP Ghrelin (80 μg/kg)	↑ latency to fall ★	vs MPTP; $p < 0.05$
	He et al. 2021	6-OHDA	↑ number of contralateral rotations and ↓ porcentage of contralateral paw use 5 weeks after 6-OHDA intoxication	vs control; $p < 0.01$
		Ghrelin (100, 200, and 400 ng)	↓ number of contralateral rotations and ↑ porcentage of contralateral paw use 5 weeks after 6-OHDA intoxication ★	vs 6-OHDA; $p < 0.01$
		6-OHDA	↑ number of complete ipsilateral rotations 3 and 4 weeks after 6-OHDA	vs Sham; $p < 0.01$ (3 weeks) and $p < 0.0001$ (4 weeks)
	Rees et al. 2023	6-OHDA	↑ number of complete ipsilateral rotations 3 and 4 weeks after 6-OHDA	vs Sham; $p < 0.01$ (3 weeks) and $p < 0.0001$ (4 weeks)
		Acyl-ghrelin	↓ number of 6-OHDA mediated rotations to a level similar to the sham-lesioned rats ★	vs Sham; $p > 0.05$
Overall metabolic and gastrointestinal status	Andrews et al. 2009	MPTP	↔ body weight	—
		Ghrelin (osmotic minipumps)	↔ body weight	—
	Karasawa et al. 2014	6-OHDA	↓ weight of fecal output at 2 and 4 h	vs vehicle; $p < 0.05$
			↓ water content of fecal output at 4 h	vs vehicle; $p < 0.05$
		Acute HM01 (3 and 10 mg/kg)	↑ fecal output at 1, 2, and 4 h (maximal effect at 3 mg/kg) ★	vs 6-OHDA; $p < 0.05$
		Acute HM01 (1 mg/kg)	↔ fecal output	—
		Acute HM01 (1, 3, and 10 mg/kg)	↑ water content ★	vs 6-OHDA; $p < 0.05$ (1 mg/kg) and $p < 0.01$ (5 and 10 mg/kg)
	Bayliss et al. 2016a	Acylated ghrelin	↑ acylated and des-acyl ghrelin in plasma ★	vs Saline/Saline; $p < 0.05$ vs Saline/MPTP; $p < 0.05$
		Des-acylated ghrelin	↑ des-acyl ghrelin in plasma	vs Saline/Saline; $p < 0.05$ vs Saline/MPTP; $p < 0.05$
		MPTP	↓ body weight, with no effect on plasma glucose	vs Saline/Saline; $p < 0.05$
		Acylated ghrelin	↔ body weight and plasma glucose	—
		Des-acylated ghrelin	↔ body weight and plasma glucose	—
		MPTP	↑ NEFA, triglycerides, and corticosterone levels in plasma	vs Saline/Saline; $p < 0.05$
		Acylated ghrelin	↔ NEFA, triglycerides, and corticosterone levels in plasma	—
		Des-acylated ghrelin	↑ corticosterone levels in plasma, with no effect on NEFA and triglycerides	vs Saline/Saline; $p < 0.05$ vs Saline/MPTP; $p < 0.05$
	Minalyan et al. 2019	6-OHDA	↓ body weight	vs vehicle; $p < 0.05$
			↔ fat mass, lean mass, and body total water	—
		HM01	↑ body weight and fat mass	vs 6-OHDA; $p < 0.05$
			↔ lean mass and body total water	—
		6-OHDA	↓ body weight, 24 h water intake, fecal output, and water content under basal conditions ★	vs vehicle; $p < 0.05$

(*continued on next page*)

Table 2 (*continued*)

Outcomes	Study	Experimental group	Main findings	Comparison
			↑ food intake under basal conditions	vs vehicle; $p < 0.05$
			↔ actual food intake when food spills were controlled under basal conditions	—
			↔ fecal pellet numbers and dried fecal weight under basal conditions	—
		6-OHDA	↓ 24 h fecal weight, fecal water and water intake 10 days after intervention	vs vehicle; $p < 0.05$
			↑ food intake 10 days after intervention	vs vehicle; $p < 0.05$
			↔ fecal pellet numbers and dried fecal weight 10 days after intervention	—
		HM01	↑ 24 h fecal weight, fecal water and water intake 10 days after intervention ★	vs 6-OHDA; $p < 0.05$
			↑ food intake 10 days after intervention	vs 6-OHDA; $p < 0.05$
			↔ fecal pellet numbers and dried fecal weight 10 days after intervention	—
	Jiao et al. 2021	P-A53T (8 weeks)	↓ body weight at 3 and 6 months of age	vs P-WT; $p < 0.0001$ and < 0.01
		G-A53T (8 weeks)	↑ body weight at 3 months of age	vs P-A53T; $p < 0.05$
		P-A53T (4 weeks)	↓ plasma total and active ghrelin levels at 3 months of age	vs P-WT; $p < 0.01$ and < 0.05
		P-A53T (8 weeks)	↓ plasma total and active ghrelin levels at 3 months of age	vs P-WT; $p < 0.01$ and < 0.05
		P-A53T (8 weeks)	↓ plasma total and active ghrelin levels at 6 months of age	vs P-WT; $p < 0.05$
		G-A53T (4 weeks)	↔ plasma total ghrelin levels at 3 months of age	—
		G-A53T (8 weeks)	↑ plasma total ghrelin levels at 3 but not at 6 months of age	vs P-A53T; $p < 0.0001$
		G-A53T (4 and 8 weeks)	↑ plasma active ghrelin levels at 3 months of age	vs P-A53T; $p < 0.05$ and < 0.001
		G-A53T (8 weeks)	↑ plasma active ghrelin levels at 6 months of age ★	vs P-A53T; $p < 0.05$
	Liu et al. 2022	G-A53T (3 weeks)	↓ stool wet weight	vs P-A53T; $p < 0.05$
		G-A53T (6 weeks)	↓ stool wet weight ★	vs P-A53T; $p < 0.01$
		G-A53T (3 weeks)	↑ stool dry weight	vs P-A53T; $p < 0.01$
		G-A53T (6 weeks)	↑ stool dry weight ★	vs P-A53T; $p < 0.001$
		G-A53T (3 weeks)	↑ stool frequency	vs P-A53T; $p < 0.01$
		G-A53T (6 weeks)	↑ stool frequency ★	vs P-A53T; $p < 0.01$
		G-A53T (3 weeks)	↔ stool water content	—
		G-A53T (6 weeks)	↔ stool water content	—
	Rees et al. 2023	6-OHDA	↔ daily food intake and food spill, but ↓ cumulative food intake	vs Sham; $p < 0.01$
		6-OHDA	↓ body weight	vs Sham; $p < 0.01$
		Acyl-ghrelin	↔ daily or cumulative food intake and food spill	—
		Acyl-ghrelin	↔ body weight	—
Overall neuroinflammatory and stress-related signaling	Karasawa et al. 2014	6-OHDA	↓ Fos-ir neurons in the arcuate nucleus, area postrema, nucleus tractus solitarius, and intermediolateral column of the lumbosacral spinal cord	vs vehicle; $p < 0.05$
		HM01 (3 mg/kg)	↑ number of c-Fos-ir in the arcuate nucleus, area postrema, and nucleus tractus solitarius ★	vs 6-OHDA; $p < 0.05$
	Wang et al. 2020	MPTP	↑ expression of α-synuclein and phosphorylated α-synuclein in the SNpc	vs control; $p < 0.01$ and < 0.05
			↑ expression of α-synuclein and phosphorylated α-synuclein in the striatum	vs control; $p < 0.01$ and < 0.001
			↑ accumulation of α-synuclein in dopaminergic neurons	vs control; $p < 0.001$
		MPTP Ghrelin (80 μg/kg)	↓ expression of α-synuclein and phosphorylated α-synuclein in the SNpc and striatum ★	vs MPTP; $p < 0.05$
			↓ accumulation of α-synuclein in dopaminergic neurons ★	vs MPTP; $p < 0.001$
Overall growth and somatic development	Rees et al. 2023	6-OHDA	↔ nose-anus, femoral, and tibial length	—
		Acyl-ghrelin	↔ nose-anus, femoral, and tibial length	—
		6-OHDA	↔ pituitary weight	—
		Acyl-ghrelin	↔ pituitary weight	—

(↑) significant increase; (↓) significant reduction; (↔) no significant difference; (★) core outcome.

4.3.4. *Autophagy regulation and α-synuclein clearance*

The autophagy process is essential for the degradation and recycling of damaged organelles and proteins, playing a fundamental role in homeostasis (Klionsky et al., 2021). Dysfunctions in this process are associated with the development of cardiovascular, neurodegenerative, metabolic, musculoskeletal, and other diseases (Klionsky et al., 2021). A recent review indicated that the contribution of impaired autophagy to the accumulation of αS is an important aspect (Nechushtai et al., 2023). Thus, the effects of ghrelin were also evaluated in this context. In one of the studies, exposure to MPTP led to reduced expression of LC3B-II and Beclin1, as well as increased p62, while treatment with ghrelin promoted the opposite effect (Wang et al., 2020). LC3B-II is one of the main markers of autophagy and reflects the level of autophagosome formation, while Beclin1 is an essential positive regulator for the initiation of the autophagic pathway (Chen et al., 2010; Liang et al., 1999). P62, in turn, functions as a selective substrate of autophagy, being recruited to the autophagosome through interaction with LC3, and is subsequently degraded in lysosomes (Mathew et al., 2009). Complementing these results, treatment with ghrelin in the 6-OHDA model also increased Atg7 expression, restored the number of lysosomes, and restored TFEB levels, a transcription factor associated with lysosomal biogenesis and function (He et al., 2021). Thus, the authors suggested

that improving autophagic flux, rather than simply activating autophagy, would promote the proper fusion of autophagosomes and lysosomes and increase αS degradation (He et al., 2021). Consequently, the reduction in αS accumulation would be achieved more efficiently.

4.3.5. Integrated mechanisms and experimental considerations

Despite the different mechanisms presented, evidence suggests that they are interconnected, with mitochondria emerging as a central feature. Although the pathogenesis of PD is complex, most animal models show some type of mitochondrial dysfunction (Lama et al., 2021). Thus, the findings collectively suggest that ghrelin plays a major role in modulating mitochondrial function, which subsequently influences redox balance, autophagic processes, and inflammation. Furthermore, these results were obtained with different doses of ghrelin. Many studies tested different doses, the route of administration depending on the experimental model. Based on the results obtained, we suggest that future studies using IP treatment for MPTP models consider doses of at least 80 μg/kg, and ICV doses for 6-OHDA models of at least 100 ng/animal. This recommendation is based on doses that have produced consistent neuroprotective effects, acknowledging that both the ideal dose and route of administration are likely to depend on the specific experimental context.

4.4. Peripheral and gastrointestinal effects

Although most studies included in this review used ghrelin as treatment, two studies evaluated the effects of the GHSR agonist HM01 and reported important peripheral results (Karasawa et al., 2014; Minalyan et al., 2019). Gastrointestinal changes are known to be one of the most common non-motor symptoms in PD and are present in 80 to 90% of individuals (Hirayama et al., 2023). In this context, in a 6-OHDA PD-induced animal model, the animals presented characteristics similar to constipation, indicating a motor alteration of the colon associated with a decrease in sacral parasympathetic flow (Karasawa et al., 2014; Minalyan et al., 2019). These results were not associated with changes in food intake, but rather with changes in water intake (Karasawa et al., 2014), which has also been observed in humans (Gan et al., 2018; Ueki and Otsuka, 2004). Intervention with HM01 had positive effects, alleviating gastrointestinal symptoms. These effects appear to be mediated at multiple levels, involving vagal afferents and brainstem circuits (area postrema), as well as activation of the lumbosacral medulla and the arcuate nucleus of the hypothalamus (Karasawa et al., 2014). Regarding water consumption, ghrelin may restore intake via the limbic reward system, with participation of the ventral tegmental area (VTA) (Minalyan et al., 2019; Stievenard et al., 2017). These results together provide key insights into the translational relevance of the 6-OHDA model and the potential peripheral action of ghrelin/HM01.

Further evidence in conditions other than PD supports the relevance of treatment with HM01. In inflammatory conditions, such as in the colon-26 tumor model, HM01 increased food consumption, body weight, muscle mass, and bone mineral density. These results were accompanied by increased hypothalamic neuronal activity (Villars et al., 2017). In a chemotherapy-induced peripheral neurotoxicity model, treatment with HM01 had a neuroprotective effect by preventing deficits in nerve conduction, mechanical hypersensitivity, and loss of intraepidermal nerve fibers (Chiorazzi et al., 2018). Following abdominal surgery, treatment with HM01 activated central vagal and enteric cholinergic neurons and reversed surgery-induced inflammation (Yuan et al., 2023). Therefore, these properties place HM01 as a promising candidate, although future studies need to continue evaluating the effects of HM01, its long-term safety, and its interaction with standard treatments for PD.

4.5. Sexual dimorphism

As seen, most of the studies included focused on acute and toxin-based PD models, while only two used progressive PD models. Interestingly, when comparing animals of different sexes at 6 months of age, this effect was specific to males, which may be associated with the neuroprotective effect of estrogen (Liu et al., 2022). In these studies, ghrelin intervention restored plasma ghrelin levels, attenuated neuron loss, and partially reduced gastrointestinal dysfunction (Jiao et al., 2021; Liu et al., 2022). As in other studies cited above, the central protective effects of ghrelin were achieved through the modulation of inflammation, via reduced microglial activation and decreased IL-6 and increased IL-10, and promotion of neuronal survival, through increased SOD1 activity and an increased Bcl-2/Bax ratio (Jiao et al., 2021).

Gender differences in the context of PD have been discussed in other studies. Evidence commonly shows that PD prevalence is higher in men, with a twofold increased risk of development (Cerri et al., 2019). However, women may have higher mortality and more rapid progression (Cerri et al., 2019). In a recent review, Zirra et al. (2023) concluded that, despite a higher prevalence in men, this proportion may vary depending on the continent, and suggested that a higher prevalence in men may have decreased in recent years (Zirra et al., 2023). Factors contributing to a higher prevalence in men include greater exposure to pesticides and lower adherence to healthy habits, including poor dietary habits, higher alcohol consumption, and smoking (Gao et al., 2007; Kim et al., 2020; Li et al., 2015; Narayan et al., 2017). Genetic factors such as alterations involving urate, LRRK2, GBA1, and GAPDH also appear to influence the differences observed between genders (Cerri et al., 2019). Differences in symptoms are observed, including motor and non-motor symptoms. While women present more dysphagia, gastrointestinal dysfunction, frequent falls, and tremors in the lower limbs, men present more drooling, camptocormia, executive function deficits, and freezing of gait (Cerri et al., 2019).

Regarding treatment, men and women may also show differences in response to pharmacological treatment and neurosurgical procedures (Georgiev et al., 2017). These variations include differences in the pharmacokinetics of levodopa, where women have greater bioavailability (Kumagai et al., 2014) and greater susceptibility than men to adverse effects when treated with high doses of levodopa (Sampaio et al., 2018). Greater efficacy of surgical therapies for improving motor symptoms has been observed in men (Roediger et al., 2019), and a greater impact of sex hormones, particularly estrogen, is expected in women (Tsang et al., 2000). Considering the differences observed in treatment with ghrelin and the low number of experimental studies that have focused on these possible differences, we suggest that future experimental studies include both sexes.

4.6. Implications and future directions

The results of this review support the notion that ghrelin has neuroprotective effects on dopaminergic neurons and enhances motor function in experimental models of PD. Moreover, the peripheral benefits of ghrelin treatment associated with the gastrointestinal system were also confirmed. However, substantial heterogeneity was observed among the studies, including the type of experimental model used, intervention characteristics (dose, route, timing, and duration), outcome measures, and biological variables. Although this heterogeneity limits the comparison and precludes definitive conclusions, it simultaneously highlights important opportunities for new studies, including *meta*-analyses incorporating sensitivity analyses such as model-specific subgroup divisions.

PD is a complex disease that affects multiple systems, and many non-motor symptoms have not been explored by the included studies. In this context, we highlight cognitive disorders, one of the most commonly observed manifestations in PD (Aarsland et al., 2021). Ghrelin has been shown to affect areas associated with cognition and emotion, including the hippocampus, and has been highlighted in conditions that also present significant cognitive impairments, such as Alzheimer's disease and diabetes mellitus (Seminara et al., 2018; Zhang et al., 2025).

Therefore, the lack of assessments in this domain represents a significant gap in the literature and also presents an important opportunity for future studies.

Other critical aspects include concomitant treatment, particularly with levodopa, and the potential negative effects of ghrelin treatment. Regarding the first aspect, only one included study evaluated concomitant treatment, combining HM01 with levodopa and carbidopa. However, this group was conducted to assess whether HM01 attenuates the adverse gastrointestinal effects induced by levodopa, which was confirmed by the study (Karasawa et al., 2014). However, whether ghrelin or GHSR agonist exerts synergistic, neutral, or antagonistic effects on the motor efficacy of dopaminergic therapies remains unknown. In addition to efficacy, the potential effects of ghrelin treatment need to be further explored. Importantly, current evidence indicates that this may be related to ghrelin isoforms. While one study suggested that the de-acylated form may cause potentially unfavorable outcomes, such as elevation of corticosterone in plasma, the acylated form has been shown to be safe for the aspects evaluated.

Future research should continue to explore: (i) the use of progressive and/or combined models to capture multiple pathological features simultaneously and improve the translational relevance of preclinical results; (ii) the assessment of sex differences, including clinical differences and responses to different treatments, especially the effects of ghrelin on disease progression; (iii) the investigation of dosage and routes of administration, considering IP, ICV, and potentially oral administration, as well as identification of optimal treatment windows (presymptomatic vs. symptomatic); (iv) the assessment of non-motor symptoms, including cognition; and (v) the evaluation of concomitant treatment with dopaminergic therapies, together with the safety profiles of different ghrelin isoforms. Clarification of these points by future work will provide the necessary basis for conducting clinical trials.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

All data generated in this review were made available in the manuscript.

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