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Ghrelin as a Neuroprotective and Palliative Agent in Alzheimer's and Parkinson's Disease

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Abstract: Ghrelin is a gastric hormone that stimulates growth hormone (GH) secretion and food intake to regulate energy homeostasis and body weight by binding to its receptor, GH secretagogue receptor (GHSR1a), which is most highly expressed in the pituitary and hypothalamus. Nowadays there is considerable evidence showing that the GHSR1a is also expressed in numerous extra-hypothalamic neuronal populations and the physiological role of ghrelin is by far wider than considered before including learning and memory, anxiety, depression and neuroprotection. The present review attempts to provide a comprehensive picture of the role of ghrelin in the central nervous system and to highlight recent findings showing its potential as an innovative therapeutic agent in neurodegenerative diseases including Alzheimer's disease and Parkinson's disease.

Keywords: Ghrelin, neuroprotection, Alzheimer's disease, Parkinson's disease, learning and memory, anxiety, depression.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, accounting for 50–60% of all cases [1]. The prevalence of AD is below 1% in individuals aged less than 65 years, but it increases to approximately 25% of the individuals aged 85 years or older in the Western world [2]. This neurodegenerative disease is associated with progressive and permanent decline in memory and overall cognitive abilities, reducing the post-diagnosis lifespan to nearly half the duration of a nondemented elderly person [3]. The first cognitive function affected is the episodic memory [4], but during the progression of the disease, attention, executive functions, semantic memory, spatial orientation and even language are deteriorated [5]. The examination of post-mortem brains of AD patients indicated the main histopathological hallmarks of the disease: the formation of senile plaques and neurofibrillary tangles, which are mainly formed due to deposition of β-amyloid (Aβ) peptides and the hyperphosphorylated tau protein, respectively [6].

Parkinson's disease (PD) is the second most common neurodegenerative disorder that affects approximately 1% of the population older than 50 years [7], and it is characterized by a slow and progressive degeneration of neuromelanin-containing dopaminergic neurons in the substantia nigra pars compacta (SNpc) with presence of eosinophillic, intracytoplasmic, proteinaceous inclusions termed as Lewy bodies and dystrophic Lewy neurites in surviving neurons [8]. At the time of diagnosis, patients typically display an array of motor impairments including bradykinesia, resting tremor, rigidity, and postural instability. Although most of the typical motor impairments are due to the loss of nigrostriatal dopaminergic neurons, PD affects multiple neuronal systems both centrally and peripherally, leading to a constellation of non-motor symptoms including olfactory deficits, affective disorders (incuding depression and anxiety), memory impairments, as well as autonomic and digestive dysfunction [9]. These non-motor features of PD do not meaningfully respond to dopaminergic medication and are a challenge to the clinical management of PD [9].

The limitations of the current pharmacological treatments of AD and PD have led to extensive investigation of novel drugs that may provide alternative or adjunctive treatment for the relief of symptoms with a reduced profile of side effects, as well as to the discovery of compounds to modify the course of these neurodegenerative diseases. The definition of neuroprotection is complex and involves the potential for preventing cell death and restoring function to damaged neurons, as well as increasing neuronal number. The development of drugs to slow or prevent the progression of AD and PD might logically evolve from an improved understanding of the etiology and pathogenesis of such diseases. There have certainly been major advances in these areas over the past few years and the prospect for the introduction of "neuroprotective" therapies is much improved. However, despite extensive efforts and research, to date, there is no proven therapy to prevent cell death or to restore affected neurons to a normal state in AD and PD. Preclinical studies in laboratory animals have provided several candidate neuroprotective drugs, but clinical endpoints are readily confounded by any symptomatic effect of the study intervention and thus do not provide an unequivocal measure of disease progression that can be used to determine if a drug has a neuroprotective effect.

In this context ghrelin, emerges a gastric hormone that stimulates growth hormone (GH) secretion and food intake to regulate energy homeostasis and body weight by binding to its receptor, GH secretagogue receptor (GHS-R1a), which is most highly expressed in the pituitary and hypothalamus. Nowadays there is considerable evidence showing that the GHS-R1a is also expressed in numerous extra-hypothalamic neuronal populations and physiological role of ghrelin is by far wider than considered before including learning and memory, anxiety, depression and neuroprotection. The present review attempts to provide a comprehensive picture of the role of ghrelin in the central nervous system (CNS) and to highlight recent

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findings showing its potential as a new palliative and neuroprotective agent in neurodegenerative diseases.

GHRELIN: HISTORICAL BACKGROUND, RECEPTOR AND FUNCTIONS

The ghrelin history began in 1977, when Frank Momany and Cyril Bowers from Tulane University (New Orleans, USA) reported a series of synthetic peptide analogs of Leu- and Met-enkephalins that specifically released growth hormone from pituitary without any opioid activity [10-12]. Surprisingly, it was found that these molecules stimulate and amplify pulsatile GH secretion, independently from GH releasing hormone (GHRH) [13]. Then, some others peptidyl derivatives with similar properties were characterized. The family of these molecules, both peptidyl and non-peptidyl compounds, has been named growth hormone secretagogues (GHSs).

GHSs are synthetic compounds that are potent stimulators of GH release, working through a G-protein-coupled receptor (GPCR), the GHS-receptor (GHS-R) [14]. Because GHSs are a group of artificial compounds and do not exist naturally, it was postulated that there must exist an endogenous ligand that binds to GHS-R and carries out similar functions to GHSs *in situ*. This makes the discovery of ghrelin an example of reverse pharmacology, starting with the synthesis of analogs and ending with the discovery of an endogenous ligand and its receptor.

A cultured cell line expressing the GHS-R was established and used to identify tissue extracts that could stimulate the GHS-R, as monitored by increases in intracellular Ca^{2+} levels. After screening several tissues, a very strong activity was unexpectedly founded in stomach [15], besides that, adenosine in hypothalamic extracts showed agonist activity on the GHS-R, and exhibited cross-desensitization with the synthetic ligands. However, in contrast to ghrelin and the synthetic GHS-R agonists, adenosine failed to stimulate GH release from pituitary cells [16]. Hence, ghrelin, as a new hormone and a closer mimetic of the synthetic GHS-R ligands, became the focus of subsequent research.

Ghrelin is a multifunctional 28-amino acid hormone produced in several tissues, with predominant source from the stomach in response to hunger and starvation by enteroendocrine X/A-like cells. However, other tissues such as ovary, placenta, kidney, pituitary gland and pancreas also produce ghrelin, although in lower amount when compared with the gastric source [17]. The ghrelin gene is expressed in the CNS, but just insignificant amounts of ghrelin can be found in rodents' neurons [18]. Nevertheless, circulating ghrelin gains access to the CNS and reached different structures as hippocampus and ventral tegmental area (VTA) [18]. The ghrelin gene was conserved throughout the evolution sharing 82.9% homology between rodents and humans, the functional 28 amino acid protein only differs by 2 amino acids between rats and humans. In humans, the ghrelin gene is located on chromosome 3p25–26 and the genomic structure of ghrelin is relatively simple and contains four prepro-ghrelin-coding exons (exon 1–4), and additional upstream exons, that codifies ghrelin and several bioactive molecules including desacyl-ghrelin and obestatin, a recent hormone with 23 amino acid ghrelin gene-derived peptide [19,20] (Fig. **1**).

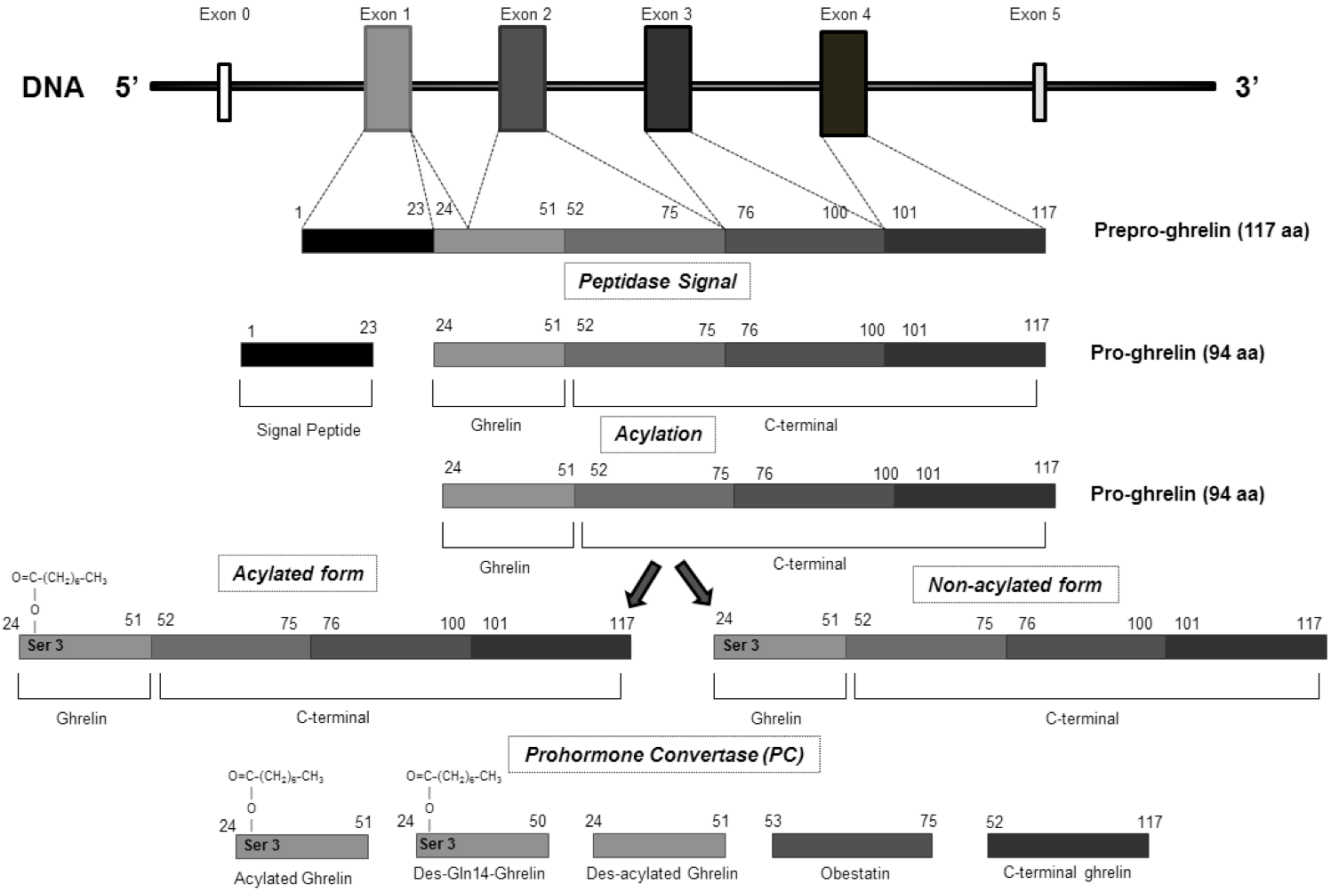

Fig. (1). Schematic representation of the post-translational processing of ghrelin. A signal peptide peptidase cleaves the signal sequence. Acylation of pro-ghrelin occurs by means of ghrelin O-acyl transferase (GOAT), which is located in the ER compartment and mediates the translocation of octanoyl-CoA. Once the pro-ghrelin precursor reaches the trans-Golgi compartment, it is cleaved by PC1/3 pro-hormone convertase. Different forms of ghrelin are released to the circulation: acylated, unacylated, and other shorter forms.

As illustrated in (Fig. **1**), during prepro-ghrelin processing, a 23 amino acid secretion-signal peptide is cleaved from the N-terminus of the 117 amino acid prepro-hormone, resulting in a 94 amino acid pro-ghrelin peptide. This 94 amino acid ghrelin pro-hormone is cleaved at Arg28/Ala29 to yield the biologically active 28 amino acid N-terminal, the ghrelin peptide, and a 66 amino acid C-terminal propeptide, C-ghrelin [21]. The prepro-ghrelin signal peptide is encoded in exon 1, and the coding sequence of the 28 amino acid ghrelin peptide hormone is encoded by parts of exons 1 and 2, the C-terminal encoded by part of exon 2, plus exons 3 and 4 of the prepro-ghrelin gene and the exon 3 codes for obestatin [19,22].

Ghrelin can be post-translationally octanoylated (acylated) at its third residue, a serine (Ser3), by ghrelin O-acyltransferase (GOAT). This enzyme belongs to a family of the membrane-bound O-acyltransferases (MBOATs) that attach fatty acids to lipids and proteins, and octanoylates pro-ghrelin before it is transported to the Golgi apparatus, where it is cleaved by pro-hormone convertase (PC) to form the mature ghrelin, but both forms desacyl and acylated can be found in circulation [23] (Fig. **1**). This n-octanoyl acylation on serine residues is unique to ghrelin and is crucial for binding, subsequent activation of the GHS-R1a and is essential for some of the hormone's bioactivity, including GH release and orexigenic effect [24].

The nonacylated form of ghrelin, des-acyl ghrelin, also exists at significant levels in stomach and blood, but the process underlying the production of des-acyl ghrelin remains unclear [25]. Des-acyl represents approximately 90% of the total ghrelin detected in serum and there is increasing evidence that the deacylation process rapidly occurs in the plasma has been responsible for the reduction in the ghrelin's half-life. However, an alternative explanation for the production of nonacylated form suggests that des-acyl ghrelin is a result of an incomplete acylation of ghrelin [26,27]. Des-acyl ghrelin and the acylated form share many nonendocrine actions, such as the stimulation of food intake, modulation of cell proliferation, and minor effects on adipogenesis, but the local where the desacylated form binds is still an open question. Baldanzi and colleagues [28] suggested the existence of another ghrelin receptor distinct from GHSR-1a. They demonstrated that ghrelin and des-acyl ghrelin recognize sites on H9c2 cardiomyocytes, which do not express the ghrelin receptor. This new receptor probably is very similar to GHSR-1a, since it differs only in its lack of ability to discriminate between the esterified and unesterified ghrelin peptides [28].

The circulating level of ghrelin is determined by the balance among its secretion and degradation rate, and its clearance by the excretion in urine [29]. Ghrelin levels also are controlled by some hormones, such as insulin and glucagon. Recently it was demonstrated that the administration of insulin in the CNS reduces serum total ghrelin concentration probably through a hypothalamus–stomach neuronal pathway [30]. Leptin is the most important signal which reflects peripheral energy balance and has opposite effects of ghrelin. While leptin decreases food intake by decreasing the neuronal activity of NPY/AGRP-containing neurons, ghrelin activates NPY/AGRP neurons stimulating food intake. Interestingly, leptin inhibits in a dose-dependent manner the ghrelin transcription *in vitro* and decreases ghrelin release from isolated rat stomach [31]. Therefore, these findings indicate that the anorexic effect of leptin may occur by decreasing ghrelin secretion.

There are two differently spliced variants of ghrelin receptor or GHS-R; the GHS-R1a and GHS-R1b. The first has features of a typical GPCR, including conserved cysteine residues in the first two extracellular loops, several potential sites for post-translational modifications (N-linked glycosylation and phosphorylation), and an aromatic triplet sequence (E/DRY) located immediately after TM-3 in the second intracellular loop. The last one is truncated and has been reported as an inactive form that fails to bind ghrelin and has no known signaling activity [32,33]. The GHS-R1a receptor is expressed in brain areas and peripheral organs including the hypothalamic arcuate nucleus (ARC), ventromedial nuclei (VMN), CA2, CA3 and detate gyrus (DG) sub-fields of the hippocampal formation, vagal afferents, pancreas, spleen, myocardium, adipose tissue, thyroid gland, adrenal gland and gastric myenteric neurons [34]. In addition, the GHS-R1a forms heterodimers with other receptors such as the cannabinoid 1 (CB1) receptor (this interaction is crucial for the appetitive effects of ghrelin) [35] and the dopamine D1 receptor (ghrelin amplifies the dopamine signaling in neurons that co-express D1 receptors) [36].

The GHS-R1a belongs to a family of receptors operating via the Gq-phospholipase C signaling pathways (Fig. **2**). The activation of the GHS-R1a receptor leads to generation of inositol triphosphate and Ca^{2+} release through the activation of the G protein $G_{\alpha q/11}$. Other signaling pathways involved with GHS-R1a activation are the extracellular signal-regulated kinase (ERK1/2), phospholipase C (PLC) and protein kinase C (PKC), and the protein kinase cascade Raf–MEK–MAPK (Fig. **2**). The interaction of ghrelin with GHS-R1a modulates different functions such as glucose homeostasis, hormone secretion, gastrointestinal motility, cell proliferation, cardiovascular, pancreatic, pulmonary and immune functions, memory, reproduction and sleep (for review see [37-39]). Taken together, these recent findings indicate that ghrelin is more than simply a natural GHS.

GHRELIN AS A NEUROPROTECTIVE STRATEGY IN NEURODEGENERATIVE DISEASES

The previous section presents evidence suggesting that the physiological role of ghrelin is by far wider than considered before and the studies in the field should not continue restricted to the investigation of ghrelin effects on the stimulation of GH secretion and regulation of food intake. As an effort to illustrate the potential of ghrelin as an innovative target for future pharmacotherapies, the next sections attempt to review the results reported in clinical and animal studies to provide a comprehensive picture of the role of ghrelin in neurodegenerative diseases.

In 2002, Frago and colleagues [40] provided the first evidence of the neuroprotective effects of ghrelin, demonstrating that the systemic administration of the GH releasing peptide-6 (GHRP-6), a synthetic ligand for the ghrelin receptor, results in increased insulin-like growth factor (IGF-I) mRNA levels and increased expression of proteins involved in cell survival and neuroprotection in several brain areas of adult rats. One year later, the same group demonstrated that the treatment with GHRP-6 decreased cell death and inhibited caspase 3 and 9 activation in the cerebellum of aged rats [41].

As summarized in Table **1**, the neuroprotective potential of ghrelin was further demonstrated by independent research groups in diverse experimental models of ischemia [42,43], traumatic brain injury (TBI) [44-46], spinal cord injury (SCI) [47,48], amyotrophic lateral sclerosis (ALS) [49,50], epilepsy [51-55], AD [56,57] and PD [58-61]. Therefore, ghrelin confers neuroprotection in diverse brain regions ranging from substantia nigra, striatum to hippocampus and cerebral cortex, and against a variety of brain noxious stimuli.

As illustrated in (Fig. **2**) and (Fig. **3**), several mechanisms have been implicated in the neuroprotective effects of ghrelin and a detailed review about this issue is beyond the scope of this article and can be found elsewhere [37,62]. At this moment, particular attention is paid to the role of ghrelin in modulating the activation of intracellular signaling cascades (such as Erk1/2, Akt1/2, PI3K and PKC pathways) that lead to the inhibition of apoptotic events, via the subsequent increase in the Bcl-2:Bax ratio, the prevention of cytochrome c release and the inhibition of caspase 3 activation [42,43,63,64]. Moreover, ghrelin prevents activation of pro-apoptotic events, such as the activation of p38 and JNK. Furthermore, ghrelin prevents inflammatory microglial activation [60] and activates the mitochondrial protein uncoupling protein-2 (UCP2)

Table 1. Overview of Ghrelin's Neuroprotective Effects in Different Experimental Models of Brain Injury.

Experimental Model	Main Findings	References
Treatment of adult rats with hormone-releasing peptide (GHRP)-6	GHRP-6, a synthetic ligand for the ghrelin receptor, increased insulin-like growth factor (IGF-I) mRNA levels in the hypothalamus, cerebellum, and hippocampus, with no effect in cerebral cortex. Phosphorylation of Akt and Bad was stimulated and the anti-apoptotic protein Bcl-2 was augmented in areas where IGF-I was increased	[40]
Treatment of aged rats with hormone-releasing peptide (GHRP)-6	GHRP-6 increased IGF-I mRNA levels, decreased cell death and inhibited caspase 3 and 9 activation in the cerebellum of aged rats	[41]
Cultured rat cortical neurons exposed to oxygen and glucose deprivation (OGD)	The neuroprotective effects of ghrelin was accompanied by an increased phosphorylation of extracellular signal-regulated kinase (ERK)1/2, Akt, and glycogen synthase kinase-3beta (GSK-3beta), suggesting the anti-apoptotic effects of ghrelin	[42]
Ischemic injury induced by transient middle cerebral artery occlusion in rats	Ghrelin protected cortical neurons against ischemic injury through the inhibition of the pro-apoptotic gene Par-4 expression and apoptotic molecules in mitochondrial pathway	[43]
Traumatic brain injury (TBI)	TBI caused significant neuronal degeneration, increased vascular permeability and increased brain cytokines TNF-α and IL-6 levels. Treatment with ghrelin mitigated these effects	[44-46]
Spinal cord injury (SCI)	Ghrelin reduced the SCI-induced oxidative stress and exert antiinflammatory effects in the rat spinal cord following trauma. However, ghrelin failed to improve the impairment of the neurological functions due to SCI	[47]
Ischemia/reperfusion (I/R) injury in the spinal cord	Ghrelin inhibited spinal I/R injury via anti-apoptotic mechanisms and improved the neurologic function in rats	[48]
Amyotrophic lateral sclerosis (ALS)	Ghrelin protected against chronic glutamate-induced cell death in organotypic spinal cord cultures (OSCC) by activating the MAPK and PI3K/Akt signaling pathways and preventing microglial activation	[49,50]
Epilepsy	Ghrelin delayed or prevented the development of seizures and hippocampal neurodegeneration in rodents induced by different compounds such as pentylenetetrazole, pilocarpine, kainic acid and penicillin	[51-55]

[59]. This protein enhances neuroprotection by decreasing the generation of reactive oxygen species (ROS) and promoting mitochondrial biogenesis [59,63] (Fig. **2**). Therefore, the common neuroprotective or neuromodulatory role of ghrelin in the brain could involve UCP2-dependent mitochondrial adaptation. Finally, these neuroprotective effects of ghrelin appear to be mediated through activation of GHSR-1a, as they were abolished by the pharmacological blockage or genetic deletion of this receptor.

These recent findings demonstrating that ghrelin is involved in neuroprotection, together with the wide distribution of ghrelin receptors in many brain areas, reinforce the idea that changes in this system could be involved in the development and/or progression of AD and PD.

Role of ghrelin in Alzheimer's disease

AD is the most prevalent age-related neurodegenerative disease that leads to cognitive impairments and dementia. The neuropathological hallmarks of AD are diffuse and neuritic plaques, which are predominantly composed of amyloid-β (Aβ) peptides, and neurofibrillary tangles composed of filamentous aggregates of hyperphosphorylated tau protein [65]. The classical Aβ cascade hypothesis in AD pathogenesis postulates that the deposition of Aβ peptides and the activation of glial cells surrounding senile plaques in brain areas involved in cognitive functions trigger marked neuronal alterations such as synaptic dysfunction, synaptic loss and neuronal death finally leading to cognitive impairments [65,66].

The first evidence showing a direct effect of ghrelin on AD-like alterations was reported in a mouse model widely used to examine the pathophysiology of early defects seen in AD. The senescence-accelerated mouse prone8 or SAMP8 mice develop early learning and memory impairments related to abnormalities in septo-hippocampal function, which are due to overproduction of β-amyloid peptides. Diano and colleagues [56] demonstrated that ghrelin improved retention of T-maze foot shock avoidance in 12 and 14 month-old SAMP8 mice. Of interest, ghrelin was found to promote both long-term potentiation (LTP) generation in hippocampal slices and the formation of spine synapses in the stratum radiatum of the hippocampal CA1 subregion, which are considered to be basic mechanisms involved in spatial lerning and memory [56] (Table **2**).

More recently, Moon *et al*. [57] investigated the effects of ghrelin on memory impairments and neuropathological alterations induced by intra-hippocampal injection of $A\beta_{1-42}$ peptide in mice. The authors reported that repeated systemic injection of ghrelin rescued $A\beta_{1-42}$-induced memory deficits evaluated in two behavioral paradigms (Y-maze and passive avoidance tasks). Moreover, ghrelin attenuated hippocampal microgliosis and neuronal loss induced by $A\beta_{1-42}$ administration [57] (Table **2**).

Corroborating these findings, unpublished results from our laboratory have indicated that the acute intracerebroventricular (i.c.v.) injection of ghrelin (3 nmol), 15 min before the infusion of $A\beta_{1-40}$ (400 pmol, i.c.v.), prevented the $A\beta_{1-40}$-induced spatial

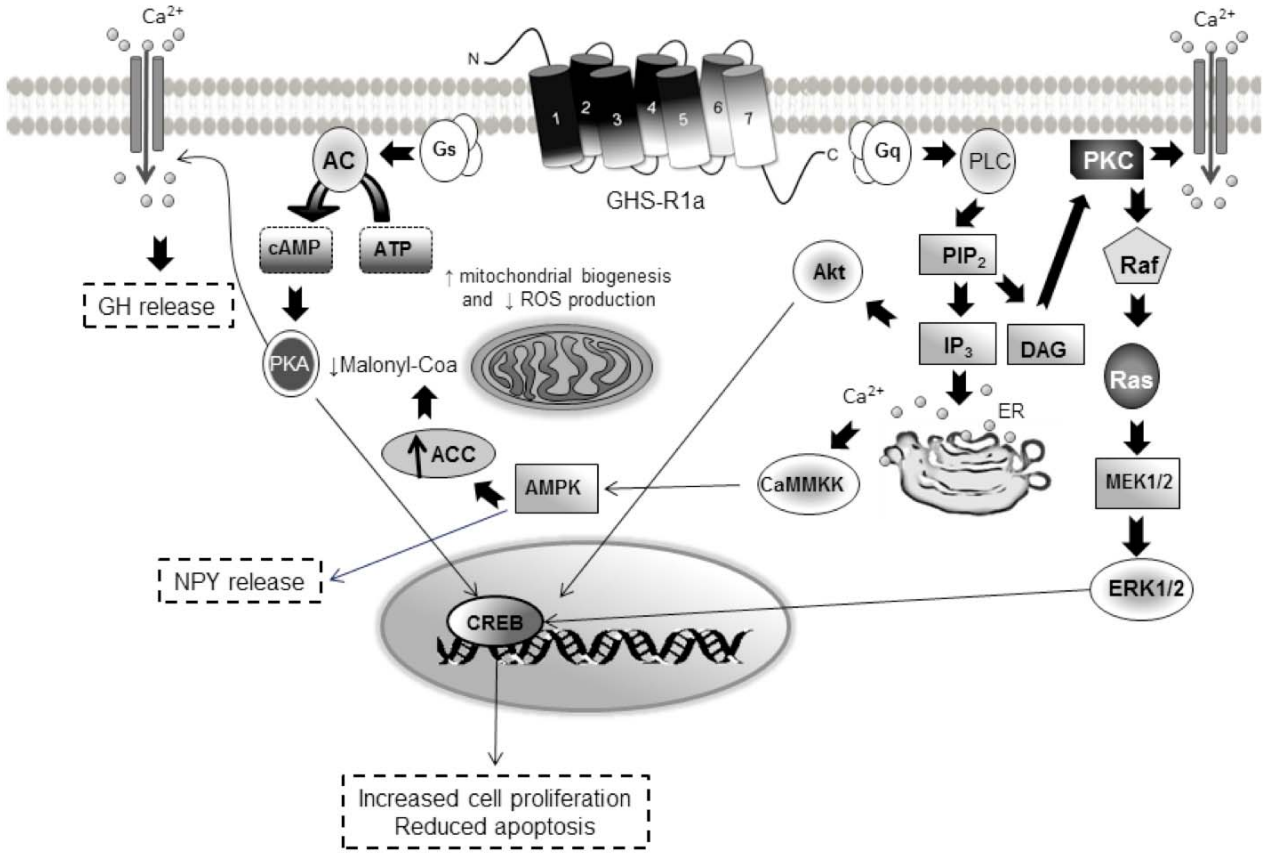

Fig. (2). Schematic illustration of the possible molecular mechanisms associated with the neuroprotective effects of ghrelin observed in experimental models of ischemia, traumatic brain injury, spinal cord injury, amyotrophic lateral sclerosis, epilepsy, Alzheimer's disease and Parkinson's disease. The interaction of ghrelin with GHS-R1a leads to activation of diverse signaling pathways including the extracellular signal-regulated kinase (ERK1/2), phospholipase C (PLC) and protein kinase C (PKC), and the protein kinase cascade Raf–MEK–MAPK. Activation of these kinase signaling pathways leads to the inhibition of apoptotic events, via the subsequent increase in the Bcl-2:Bax ratio, the prevention of Cyt release and the inhibition of caspase 3 activation. Furthermore, ghrelin prevents inflammatory microglial activation and activates the mitochondrial protein uncoupling protein-2 (UCP2). This protein enhances neuroprotection by suppressing reactive oxygen species (ROS) and promoting mitochondrial biogenesis.

memory impairments and depressive-like behaviors in adult Swiss mice evaluated in the object location and forced swimming task, respectively. Moreover, ghrelin mitigated a series of neurochemical changes induced by i.c.v. infusion of $A\beta_{1-40}$, including the increase of oxidative stress biomarkers and acetylcholinesterase (AChE) activity and the decrease of glutamate uptake in the hippocampus and frontal cortex of mice (Table **2**). Finally, ghrelin (1 nM) was found to prevent the impairments on LTP generation induced by $A\beta_{1-40}$ (200 nM) in the CA1 subregion of hippocampal slices of mice (Santos *et al*., unpublished data) (Table **2**).

Altogether, these results suggest that ghrelin may counteract neurotoxic effects of Aβ peptides by reducing excitotoxicity, neuroinflammation, oxidative stress and activation of apoptotic cell death mechanims. Moreover, the ghrelin's effects on AChE activity and LTP generation may represent potential mechanisms responsible for its cognitive enhancing properties (Fig. **3**). A better understanding of how the multiple actions of ghrelin influence survival of neurons might further consolidate ghrelin as a potential neuroprotective agent for the treatment of AD.

At this moment, few clinical studies have attempted to comprehend the potential implication of the ghrelin system in human AD (Table **2**). In 2002, it was reported that mean plasma ghrelin concentrations in older normal weight subjects were significantly lower than those observed in young normal weight subjects, providing the first evidence for an age-related decline of peripheral ghrelin concentrations [67]. Nevertheless, Proto *et al*. [68] reported that ghrelin levels do not vary in the cerebrospinal fluid of AD patients when compared with age-matched controls. In a recent study, Castaño's group (University of Córdoba, Spain) analyzed the mRNA expression of the ghrelin system in three different regions of the temporal gyrus (inferior, medial and superior) of control and AD human brains, since it is one of the most affected memory-related regions in AD. This study showed, for the first time, that AD patients have a reduction in local brain ghrelin production, as compared with age-matched controls [69].

In addition, Shibata *et al*. [70] investigated whether single nucleotide polymorphisms (SNPs) of the ghrelin gene are associated with AD in a Japanese population. A total of 182 AD patients and 143 age-matched controls were included in this study and the SNPs were genotyped using TaqMan technology and were analyzed using a case-control study design. The authors observed that one SNP, rs4684677 (Leu90Gln), showed a marginal association with age of AD onset, but no additional association between other SNPs of the ghrelin gene and AD were detected [70] (Table **2**). Moreover, Theodoropoulou *et al*. [71] investigated recently the potential relationship between serum ghrelin levels and weight loss in patients with AD. The authors reported that the area-under-the-curve (AUC) for serum ghrelin levels after 75 g of glucose load is lower in male patients with AD compared to control males, while no difference was observed between females AD and controls. Therefore, the

Table 2. Overview of the Role of Ghrelin in Experimental Models and Human Alzheimer's Disease (AD).

Experimental Model	Main Findings	References
Senescence-accelerated mouse prone8 (SAMP8 mice)	Ghrelin improved retention of T-maze foot shock avoidance in 12 and 14 month-old SAMP8 mice. Moreover, ghrelin promoted dendritic spine synapse formation and generation of long-term potentiation (LTP) in the hippocampus of mice. Disruption of the gene that encodes ghrelin resulted in decreased numbers of spine synapses in the CA1 region and impaired performance of mice in the T-maze foot shock avoidance task. Ghrelin administration reversed these alterations	[56]
Intra-hippocampal injection of $A\beta_{1-42}$ peptide in ICR mice	Intraperitoneal injection of ghrelin (80 μg/kg) improved $A\beta_{1-42}$ (10 μM, 3 μl)-induced memory deficits evaluated in the Y-maze and passive avoidance tasks. Moreover, ghrelin attenuated hippocampal microgliosis and neuronal loss induced by $A\beta_{1-42}$ administration	[57]
Intracerebroventricular injection of $A\beta_{1-40}$ peptide in Swiss mice	Ghrelin (3 nmol, i.c.v.) prevented the $A\beta_{1-40}$ (400 pmol, i.c.v.)-induced spatial memory impairments and depressive-like behaviors evaluated in the object location and forced swimming tasks. Moreover, ghrelin mitigated the increase of oxidative stress biomarkers and acetylcholinesterase (AChE) activity and the decrease of glutamate uptake in the hippocampus and frontal cortex of mice	Santos *et al*., unpublished data
Hippocampal slices of Swiss adult mice	Ghrelin (1 nM) prevented the impairments on LTP generation induced by $A\beta_{1-40}$ (200 nM) in the CA1 subfield of hippocampal slices of adult mice	Santos *et al*., unpublished data
12 young and 7 old normal weight subjects	Mean plasma ghrelin concentrations in older normal weight subjects were significantly lower than those present in young normal weight subjects	[67]
14 AD patients	Ghrelin levels in the cerebrospinal fluid of AD patients were similar to those of age-matched controls	[68]
Analysis of temporal lobe of 6 patients with AD and 6 non-demented controls obtained from the Netherlands Brain Bank	mRNA levels for ghrelin, ghrelin-O-acyltransferase (enzyme responsible for ghrelin acylation), and its receptor GHS-R1a were reduced, while expression of GHS-R1b increased, in the temporal lobe of AD patients	[69]
182 AD patients and 143 age-matched controls	One single nucleotide polymorphisms (SNP), rs4684677 (Leu90Gln), showed a marginal association with age of AD onset, but no additional association between other SNPs of the ghrelin gene and AD were detected	[70]
27 AD patients and 23 age-matched controls	The area-under-the-curve (AUC) for serum ghrelin levels after 75 g of glucose load was lower in male patients with AD compared to control males, while no difference was observed between females AD and controls	[71]

disruption of the normal compensatory modulation of ghrelin secretion might contribute to the metabolic changes (e.g., lower lean mass content) observed in male patients with AD [71] (Table **2**). However, it must be conceded that further multifactorial studies are needed to clarify the relationship between ghrelin and AD.

Role of Ghrelin in Parkinson's Disease

Classically, PD is considered to be a motor system disease and its diagnosis is based on the presence of a set of cardinal motor signs (e.g. rigidity, bradykinesia, rest tremor and postural reflex disturbance). These symptoms of PD mainly result from the progressive degeneration of dopamine neurons of the SNpc, which causes a consequent reduction of dopamine levels in the striatum [8]. Dopamine-replacement therapy has dominated the treatment of PD since the early 1960s and although the currently approved anti-parkinsonian agents offer effective relief of the motor deficits, especially in the early-moderate stages of the disease, they have not be found to alleviate the underlying dopaminergic neuron degeneration and drug efficacy is gradually lost [72]. Moreover, another major limitation of chronic dopaminergic therapy is the numerous adverse effects such as the development of abnormal involuntary movements (namely dyskinesia), psychosis and behavioral disturbance (e.g., compulsive gambling, hypersexuality) [73].

Dopamine replacement therapy is based on the importance of nigral dopaminergic cell loss, the ensuing striatal dopamine depletion, and onset of motor symptoms. However, the neurodegenerative processes that lead to sporadic PD begin many years before the appearance of the characteristic motor symptoms and additional neuronal fields and neurotransmitter systems are also involved in PD, including the anterior olfactory structures, dorsal motor nucleus of vagus, caudal raphe nuclei, locus coeruleus, the autonomic nervous system, hippocampus and the cerebral cortex [74]. Accordingly, cholinergic, adrenergic and serotoninergic neurons are also lost which seems to be responsible for the non-motor symptoms of PD encompassing olfactory and memory impairments, sleep abnormalities and depression, as well as gastrointestinal disturbance, which precede the classical motor symptoms [9]. Non-motor features of PD invariably do not respond to dopaminergic medication and probably form the major current challenge faced in the clinical management of PD [9].

Therefore, the limitations of the current pharmacological treatment of PD have led to extensive investigation of novel non-

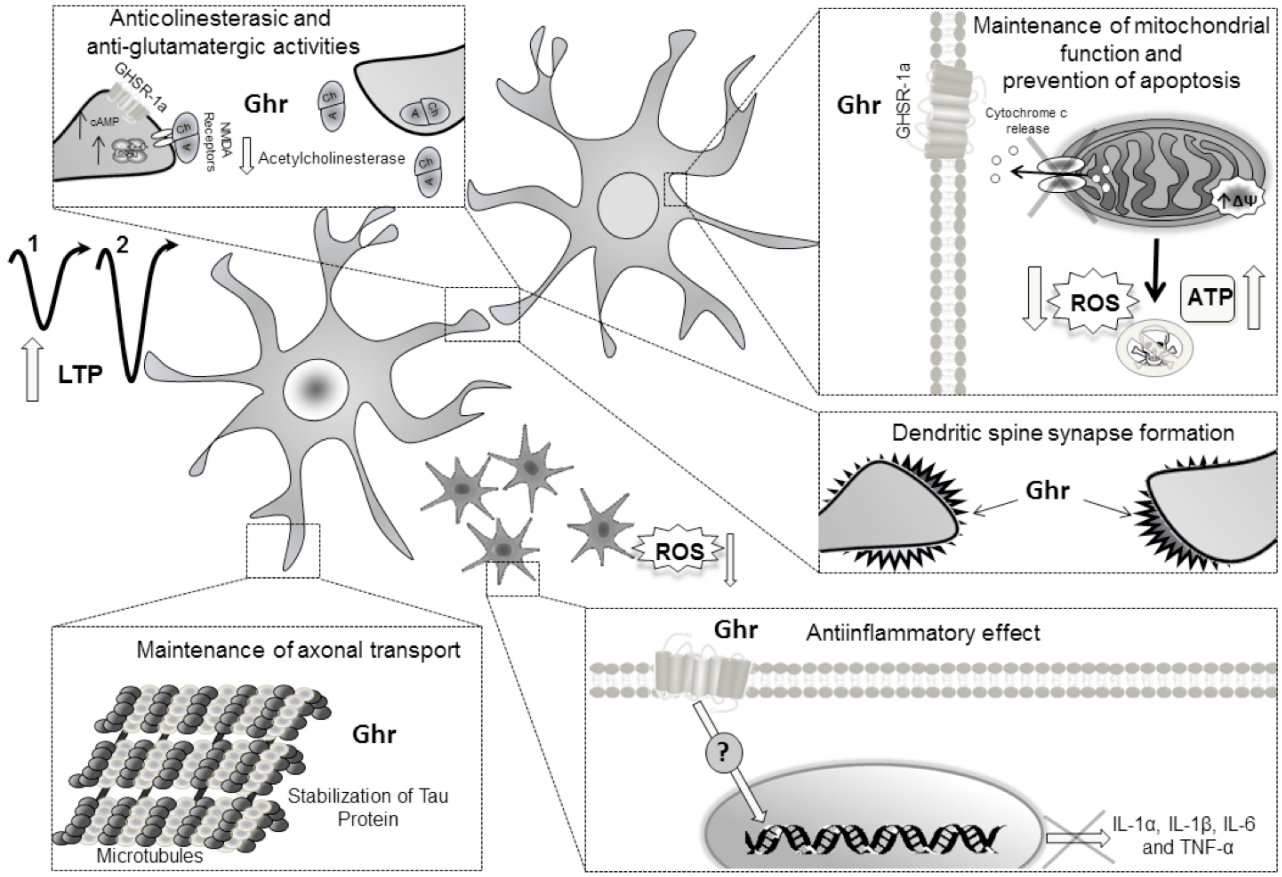

Fig. (3). Schematic illustration of the possible molecular mechanisms associated with the neuroprotective and cognitive enhancing properties of ghrelin observed in experimental models of Alzheimers's disease. Ghrelin mitigates a series of neurochemical changes induced by infusion of amyloid-beta (Aβ) peptides including microgliosis, neuronal loss, increase of oxidative stress biomarkers, increase of acetylcholinesterase (AChE) activity, decrease of glutamate uptake and impairments on long-term potentiation (LTP) generation in the hippocampus and frontal cortex of mice.

dopaminergic drugs that may provide alternative or adjunctive treatment for both motor and non-motor symptoms relief with a reduced side-effect profile as well as the discovery of compounds to modify the course of PD. Over the last years, several lines of evidence have suggested the potential of ghrelin in the treatment of PD and an increasing number of studies have investigated the effects of ghrelin in different animal models and PD patients (Table **3**).

Experimental models of PD have attempted to reproduce the pathogenic process and to involve areas of the brain pathologically affected in humans. Pathogenic modeling has been attempted using a range of toxins, as well as through the use of transgenic models of gene defects in familial PD and mutant rodent strains. However, there are still no accepted progressive models of PD that mimic the processes known to occur during cell death and that result in the motor and non-motor deficits, pathology and biochemistry features, and drug responsiveness as seen in humans (for recent review see [75]). Despite these limitations, over the past couple of decades, the proneurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has become a widely used approach for modeling PD. In humans and non-human primates, MPTP causes a severe and irreversible PD-like syndrome [76]. Although rodents are less sensitive to MPTP toxicity, largely because of the economic, logistic, and ethical constraints related to experimental research in primates, the MPTP mouse model has become the most commonly used animal model of PD [77].

The MPTP toxicokinetics is complex and has several stages, and the pathogenic mechanisms involved in the neurodegeneration induced by MPTP include mitochondrial dysfunction, oxidative stress, activation of apoptotic cell death mechanisms and glutamatergic excitotoxicity (for review see [78]). Jiang and co-workers [58] published a pioner study investigating whether ghrelin protects the dopaminergic neurons from MPTP insult *in vivo*. C57BL6 mice were pretreated with different doses of ghrelin (50, 100, 200 or 400 ng/mouse, i.c.v.) once per day for 8 consecutive days, and received MPTP (30 mg/kg, i.p.) for the last 5 days. The authors described that ghrelin, acting through GHS-R1a, inhibited MPTP-induced dopaminergic neuronal loss in the SNpc as well as dopamine depletion in the striatum [58]. Further *in vivo* [59,60] and *in vitro* [61] studies have confirmed the capability of ghrelin to protect dopaminergic neurons against the toxicity induced by MPTP (Table **3**), suggesting its potential as a new neuroprotective agent in PD.

Although the sequence of events leading to the protective effects of ghrelin against the loss of dopaminergic neurons has not been fully elucidated, several mechanisms have been implicated in these effects. Ghrelin attenuates MPTP-induced caspase 3 activity by regulating intracellular apoptotic signaling molecules, such as Bcl-2 and Bax [58,61] (Table **3**). Consistent with the known antiinflammatory effects of ghrelin in the periphery, inflammatory markers such as activated microglia, tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β) were significantly inhibited by ghrelin in the substantia nigra and striatum of MPTP-treated mice [60] (Table **3**).

In addition, the Andrews' group (Monash University, Australia) published a highlight study demonstrating that the systemic administration of ghrelin could reduce the MPTP-induced dopamine cell loss in the substantia nigra of mice by increasing mitochondrial

Table 3. Overview of the Role of Ghrelin in Experimental Models and Human Parkinson's Disease (AD).

Experimental Model	Main Findings	Reference
C57BL6 mice were pretreated with different doses of ghrelin (50, 100, 200 or 400 ng/mouse, i.c.v.) once per day for 8 consecutive days, and received MPTP (30 mg/kg, i.p.) for the last 5 days	Ghrelin, acting through GHS-R1a, inhibited MPTP-induced dopaminergic neuronal loss in the substantia nigra pars compacta (SNpc) as well as striatal dopamine depletion. Ghrelin also reversed the downregulation of Bcl-2, the upregulation of Bax, and caspase-3 activation caused by MPTP	[58]
In vitro studies with MES23.5 cells treated with 1-methyl-4-phenylpyridinium (MPP^+)	MES23.5 cells treated with 200 micromol/L of MPP^+ showed decreased cell viability and mitochondrial transmembrane potential, an elevated level of reactive oxidative species production and activation of caspase-3 and apoptotic morphological changes. Pretreatment with ghrelin abolished the MPP^+-induced apoptotic changes in a concentration-dependent manner	[61]
C57BL6 received four intraperitoneal (i.p.) injections of MPTP (20 mg/kg) at 2-h intervals in a single day, and they were administered with ghrelin (20, 40, 80, or 160 μg/kg, i.p.) 2 h before the first MPTP injection and 30 min prior to each MPTP injection for a total of five injections	Ghrelin attenuated the loss of SNpc neurons and the striatal dopaminergic fibers through the activation of GHS-R1a. Ghrelin also reduced nitrotyrosine levels and improved the impairment of rota-rod performance. Furthermore, ghrelin prevented MPTP-induced microglial activation in the SNpc and striatum, the expression of pro-inflammatory molecules TNF-α and IL-1β, and the activation of inducible nitric oxide synthase	[60]
C57/B6, UCP2 knockout and ghrelin knockout mice were injected with MPTP (40 mg/kg, i.p.)	Ghrelin knockout mice were more susceptible to dopamine cell loss in the SNpc and dopamine depletion in the striatum after MPTP administration than wild type controls. Ghrelin increased the firing rate of SNpc dopamine neurons, which enhances dopamine availability during the course of degeneration and lowers the loss of dopamine levels in the dorsal striatum. Moreover, ghrelin enhanced the uncoupling protein 2 (UCP2)-dependent mitochondrial respiration and proliferation, providing a bioenergetic status that makes these neurons more resistant to cellular stress	[59]
12 PD patients taking chronic L-DOPA therapy and 12 PD patients with subthalamic nucleus deep-brain stimulation (STN-DBS) therapy associated with chronic L-DOPA treatment	L-DOPA treatment did not have a significant acute effect on ghrelin levels either in L-DOPA-alone patients or in the STN-DBS patients off neurostimulation. Moreover, STN-DBS itself did not elicit a modification of ghrelin levels in STN-DBS patients off L-DOPA	[79]
11 PD patients with unintentional weight loss, 16 PD patients without weight loss and 12 controls	The body mass index (BMI) was lower in all PD patients (with and without the weight loss) and in PD patients with the weight loss in comparison to the control group, however, there was no difference between both groups of PD patients. BMI was positively correlated with plasma active ghrelin concentration. The lower BMI was, the lower plasma active ghrelin concentration was in PD patients with the weight loss	[80]
39 (including 19 drug-naïve) PD patients, 11 idiopathic REM sleep behaviour disorder (iRBD) patients and 20 healthy controls	Controls showed a decrease of mean fasting ghrelin serum concentrations in the early postprandial phase, followed by a recuperation starting 60 min after the test meal and reaching a maximum at 300 min. The dynamic regulation of ghrelin in response to food intake is partially impaired in subjects at putative preclinical (iRBD) and clinical stages of PD. Thus, the impaired ghrelin excretion might qualify as a peripheral biomarker and be of diagnostic or therapeutic value	[81]
23 PD patients were submitted for body composition measurements and blood sampling 3 days before, and 3 and 6 months after STN-DBS	Weight gain was significantly associated with the increase of peripheral concentrations of ghrelin at 6 months after STN-DBS	[82]

respiration via uncoupling protein 2 (UCP2) [59]. The same group showed previously the crucial role of UCP2 for nigrostriatal dopaminergic neuronal function and protection against MPTP-induced neuronal degeneration [83]. The crosstalk between ghrelin and dopamine was predictable based on interactions between the GHS-R and dopamine D1 receptor signaling pathways. Previous studies showed that ghrelin administration could increase extracellular concentration of dopamine in the nucleus accumbens [84]. GHS-R1a is abundantly expressed in dopaminergic neurons in the substantia nigra and ghrelin knockout mice were more susceptible to dopamine cell loss in the SNpc and dopamine depletion in the striatum after MPTP administration than wild type controls [59] (Table **3**). Altogether, the data reviewed here reveal that peripheral ghrelin plays an important role in the maintenance and protection of normal nigrostriatal dopamine function and suggest that ghrelin may be a valuable therapeutic agent for neurodegenerative diseases such as PD.

Patients with PD frequently experience weight loss that may be related to different factors: gender, age, physical activity, gastrointestinal dysfunction, disease duration and pharmacological treatment (L-DOPA therapy) [85]. Subthalamic nucleus deep-brain stimulation (STN-DBS) is an alternative to L-DOPA therapy, improving both PD and motor fluctuations [86]. Interestingly, patients with PD gain weight after STN-DBS [87,88]. Considering that STN-DBS electrodes are located close to the hypothalamic centre regulating feeding behaviour, and ghrelin is secreted by the hypo-

thalamic neurones [89], and among other functions, ghrelin is involved in the homeostatic regulation of appetite and energy balance, Corcuff *et al.* [79] investigated possible changes on serum ghrelin levels in PD patients treated with STN-DBS and/or L-DOPA. In this study, all patients were investigated before and after receiving dopamine treatment, and the group of patients with an implanted neurostimulator was investigated with and without ongoing neurostimulation. The results indicated that L-DOPA treatment did not have a significant acute effect on ghrelin levels either in L-DOPA-alone patients or in the STN-DBS patients off neurostimulation. Moreover, STN-DBS itself did not elicit a modification of ghrelin levels in STN-DBS patients off L-DOPA. Therefore, the authors concluded that total circulating ghrelin does not play an important role in the modification of weight homeostasis in PD patients treated with STN-DBS [79] (Table **3**).

More recently, Markaki *et al.* [82] investigated a possible involvement of ghrelin in the weight gain of PD patients after STN-DBS. Twenty-three PD patients were submitted for body composition measurements and blood sampling 3 days before, and 3 and 6 months after STN-DBS. Weight gain was significantly associated with the increase of peripheral concentrations of ghrelin at 6 months after STN-DBS. Therefore, contrasting with the previous observations by Corcuff *et al*. [79], STN-DBS seems to temporarily dysregulate the hypothalamic secretion of ghrelin that may be responsible for the weight gain of PD patients after STN-DBS [82]. Moreover, the authors of this study emphasize that a possible neuroprotective role of DBS, exerted through the increase of ghrelin levels, should be further investigated.

In another study, Fiszer *et al.* [80] measured the plasma active ghrelin concentration in 11 PD patients with unintentional weight loss, 16 PD patients without weight loss and 12 controls. The body mass index (BMI) was lower in all PD patients investigated (with and without the weight loss) and in PD patients with the weight loss in comparison to the control group. However, there was no difference between both groups of PD patients. BMI was positively correlated with plasma active ghrelin concentration. Interestingly, the lower BMI was, the lower plasma active ghrelin concentration was in PD patients with the weight loss [80] (Table **3**).

As stated before, besides motor symptoms, PD patients frequently exhibit non-motor symptoms such as hyposmia, REM sleep behaviour disorder (RBD) and disturbed gastrointestinal motility [90-92] very early in the course of the disease. In relation to the gastrointestinal tract, the stomach has been proposed as one possible ignition point of PD related neuropathology. In respect to the sleep disorder iRBD, about two-thirds of patients with idiopathic RBD (iRBD) develop the alpha-synucleinopathy PD over time [93,94]. Therefore, iRBD is considered a putative pre-motor stage of PD. In this context, Unger *et al*. [81] measured fasting and postprandial total ghrelin serum concentrations in 20 healthy controls, 39 (including 19 drug-naïve) PD patients and 11 iRBD patients. Controls showed a decrease of mean fasting ghrelin serum concentrations in the early postprandial phase, followed by a recuperation starting 60 min after the test meal and reaching a maximum at 300 min. The dynamic regulation of ghrelin in response to food intake is partially impaired in subjects at putative preclinical (iRBD) and clinical stages of PD (Table **3**). The authors speculate that reduced ghrelin excretion might increase the vulnerability of nigrostriatal dopaminergic neurons in PD patients as suggested by animal studies. Finally, the impaired ghrelin excretion might qualify as a peripheral biomarker and be of diagnostic or therapeutic value [81].

GHRELIN AS A PALLIATIVE TREATMENT FOR THE MEMORY IMPAIRMENTS IN NEURODEGENERATIVE DISEASES

The increasing incidence of neurodegenerative diseases that involve the deterioration of cognitive function has led the scientific community to explore the underlying mechanisms of memory processes and possible novel therapeutic strategies to enhance learning and memory. In this context, ghrelin and GSH-R1a agonists emerge as potential palliative treatments for memory loss that accompanies aging as well AD and PD. Ghrelin and memory story starts silently in 1997 when Guan and colleagues [34] wrote about GHS receptors: "*In addition to the hypothalamus, mRNA encoding the GHS-R was also expressed in several other discrete regions of the rat brain. For example, specific signals were detected in the dentate gyrus, CA2 and CA3 regions of the hippocampal formation…. The functional significance of the GHS-R in these brain regions is not clear at this time… results described above revealed hypothalamus, hippocampal formation and pituitary as the regions with the most abundant expression of GHS-R mRNA.*"

Latter, this G-protein coupled receptor was deorphanized by Kojima *et al*. [15] that discovered the 28 amino acid octanoylated peptide ghrelin. Taking in mind the Guan´s results about the distribution of ghrelin receptors, and the pivotal role of hippocampus on learning and memory, de Barioglio's group in the Universidad Nacional de Córdoba (Córdoba, Argentina) started the investigation of the putative role of ghrelin on memory in laboratory animals. Ghrelin was injected by i.c.v. route in rats and their performance in the open-field, plus-maze, and step-down inhibitory avoidance tasks was analyzed. The administration of ghrelin increased in a dose-dependent manner the latency to step-down in the test session, showing for the first time that ghrelin increases memory retention, possible through a hippocampal-dependent mechanism [95] (Table **4**). Nevertheless, it is well known that the i.c.v. injection ensures that the peptide effects are centrally mediated but provide mere hints about their site of action.

In this context, localized and precise microinfusions in specific brain regions provide relevant information about "where" the processes under investigation occur. Then, in the next set of experiments the same research group identified extrahypothalamic targets for ghrelin that could justify the changes in the expression of anxiety-like behavior as well as the increase in memory retention induced by the peptide. Thus, ghrelin was injected into brain structures such as the hippocampus, amygdala and dorsal raphe nucleus (DRN). The results suggested differential roles of the peptide in those structures in the regulation of memory, feeding, and anxiety-like behaviors [96]. Ghrelin administration in all these three regions clearly increased memory retention in a dose-dependent manner. Food intake increased in relation to control rats when ghrelin was injected in the hippocampus and DRN, but injections into the amygdala did not affect food intake [96]. The assumption that the increase in the latency time into the step-down could therefore be attributed to an anxiogenic effect of ghrelin was also clarified and the authors showed that the ghrelin's doses that improved memory retention of rats did not produce any anxiogenic-like behavior [96].

More recently, Carlini *et al.* [97] demonstrated that the memory enhancing properties of ghrelin can be also observed in a novel object recognition task in mice submitted to 28 days of 50% food restriction. This task differs from the step-down inhibitory avoidance task on the type of information that must be remembered since during the test session of the step-down task, the animals remember the footshock in association with the context. Thus, both paradigms evaluate memory retention but step-down evaluates a memory for aversive stimulus whereas the object recognition test evaluates just the ability to recognize objects. Likewise in mice, decreases in object recognition performance due to chronic food restriction were counteracted by ghrelin administration [97]. As recently reviewed by Gahete *et al.* [98], further studies have confirmed and extended the capability of ghrelin to improve learning and memory processes in laboratory animals (Table **4**).

In line with the above mentioned findings, in 2006, the Horvath's group (Yale University School of Medicine, New Haven, USA) published very exciting results showing that circulating ghrelin crosses the blood–brain barrier, enters into the hippocampus and

Table 4. Summary of Ghrelin's Effects on Learning and Memory.

Experimental Model	Main Findings	References
Male Wistar rats were injected by intracerebroventricular (i.c.v.) route with ghrelin (0.3, 1.5, and 3 nmol/µl) and immediately later they were tested in the open field, elevated plus-maze and step-down inhibitory avoidance tasks	Ghrelin increased freezing in the open field and decreased the number of entries and the time spent on the open arms in the elevated plus-maze, indicating an anxiogenic effect. Moreover, ghrelin increased in a dose-dependent manner the latency time in the step-down test. A rapid and prolonged increase in food intake was also observed. These results indicate that ghrelin induces anxiogenesis and increases memory retention in rats	[95]
Male Wistar rats were microinjected bilaterally with ghrelin (0.3, 1.5, and 3 nmol/µl) into the hippocampus, amygdala or in dorsal raphe nucleus (DRN) and immediately later they were tested in the elevated plus-maze and step-down inhibitory avoidance tasks	The injection of ghrelin into the hippocampus and DRN, but not into the amygdala, increased food intake. Ghrelin dose dependently increased memory retention in the hippocampus, amygdala, and DRN. Moreover, ghrelin at different potencies induced anxiogenesis in these brain structures	[96]
Wild-type (C57BL6), ghrelin knockout and CD-1 mice were subcutaneously (s.c.) injected with ghrelin (10 µg/kg) or the ghrelin mimetic LY444711 (5 mg/kg) and were tested in the spontaneous alternation plus-maze, T-maze footshock avoidance and step-down inhibitory avoidance tasks	Ghrelin enters the hippocampus and binds to neurons of the hippocampal formation, where it promotes dendritic spine synapse formation and generation of long-term potentiation. These ghrelin-induced synaptic changes are paralleled by enhanced spatial learning and memory. Targeted disruption of the gene that encodes ghrelin resulted in decreased numbers of spine synapses in the CA1 region and impaired performance of mice in behavioral memory testing, both of which were rapidly reversed by ghrelin administration	[56]
Male Wistar rats were pretreated intraperitoneally (i.p.) with the selective serotonin reuptake inhibitors fluoxetine (5 mg/kg) or clomipramine (2.5 or 5 mg/kg) and 30 min later they were microinjected bilaterally with ghrelin (0.03, 0.3 and 3.0 nmol/µl) into the CA1 hippocampus or i.c.v. and immediately later they were tested in the step-down inhibitory avoidance task	Ghrelin increased food intake and the short and long term memory retention and these effects were prevented by the pretreatment with fluoxetine. These results suggest that the effects of ghrelin on both feeding and memory retention in extrahypothalamic structures such as the hippocampus, could depend on the availability of serotonin	[99]
Female Swiss-SWR/J mice submitted to 28 days of 50% food restriction were microinjected bilaterally with ghrelin (0.03, 0.3 and 3.0 nmol/µl, i.c.v.) and immediately later they were tested in the novel object recognition task	The animals with food restriction showed an increase in plasma ghrelin levels and a decrease in the percentage of novel object recognition time. The i.c.v. administration of ghrelin improved the memory impairments of food-restricted animals	[97]
Male Lister hooded rats were injected with the structurally non-peptide ghrelin receptor agonists GSK894490A (0.3 and 3.0 mg/kg p.o.) and CP-464709-18 (1 and 3 mg/kg s.c.) and were tested in the novel object recognition test, a modified water maze paradigm and a scopolamine-induced deficit in cued fear conditioning	Both compounds significantly improved performance in the novel object recognition and modified water maze tests but were unable to attenuate a scopolamine deficit in cued fear conditioning	[100]
Male Wistar rats were microinjected bilaterally with ghrelin (0.03, 0.3 and 3.0 nmol/µl) into the CA1 hippocampus or i.c.v. 15 min previous the training session or 15 min previous the test session (performed 24 h after training) of the setp-down inhibitory avoidance task	Intra-hippocampal ghrelin administration previous the training session improved the long-term memory in this task, but did not modify the short-term memory. Ghrelin administration previous the test session did not alter the memory performance. These results suggest that ghrelin may modulate specific molecular signaling involved in memory acquisition/consolidation but not in the retrieval	[101]
Male Wistar rats were injected into the hippocampus with ACSF, L-NOArg (2 µg/µl), ghrelin (0.3 or 3.0 nmol/µl) or L-NOArg prior to ghrelin administration, immediately after training in the step-down. Thirty minutes later, the animals were sacrificed and the nitric oxide synthase (NOS) activity and electrophysiological paramameteres were measured in the hippocampus	Intra-hippocampal ghrelin administration increased the NOS activity in a dose-dependent manner, and reduced the threshold for LTP generation in dentate gyrus of rat hippocampus. Moreover, pre-administration of L-NOArg in the hippocampus partially prevented the ghrelin-induced memory improvement, abolished the increase in NOS activity, and prevented the decreased threshold to generate LTP induced by ghrelin. These findings suggest that activation of the NOS/NO pathway in hippocampus participates in the effects of ghrelin on memory consolidation	[102]
Male Wistar rats were bilaterally injected into the dorsal hippocampus with 1 nM of ghrelin (5 µL) and/or 1 µM of LY294002 (3 µL), a phosphoinositide 3-kinase (PI3K) inhibitor, once a day for 4 days and were later tested in the Morris water maze	Ghrelin infusion prolonged expression of LTP and induced long-lasting potentiation in the dentate gyrus (DG) *in vivo*. This potentiation was inhibited by PI3K antagonists. This dose of ghrelin time-dependently enhanced the phosphorylation of Akt-Ser473, a downstream molecule of PI3K. In addition, ghrelin infusion into the hippocampus improved water maze performance. These results suggest that ghrelin infusion into the hippocampus may activate the PI3K signaling pathway, and enhance synaptic plasticity and spatial memory	[103]
Congenic *ghsr*$^{-/-}$ mice on the C57BL6/J background were subjected to a battery of behavioral tests including rota-rod, hot plate, open field, Morris water maze and fear conditioning tasks	*ghsr*$^{-/-}$ mice exhibited normal balance, movement, coordination, and pain sensation. Interestingly, the genetic deletion of GHS-R1a has opposing regulatory effects on learning and memory. While spatial memory was improved in the *ghsr*$^{-/-}$ mice, contextual memory was impaired by the lack of this receptor	[104]

binds to neurons of the hippocampal formation, promoting dendritic spine synapse formation and generating LTP [56]. In this same study, the authors demonstrated that the subcutaneous (s.c.) administration of ghrelin or the ghrelin mimetic LY444711 led to a marked improvement in spatial memory retention in mice. In addition, ghrelin knockout mice presented a reduced number of spine synapses in the hippocampal brain region as well as displayed impaired performance in learning and memory paradigms [56] (Table **4**). Moreover, Atcha *et al*. [100] demonstrated that the oral or s.c. administration of two structurally non-peptide ghrelin receptor agonists (GSK894490A and CP-464709-18) readily cross the blood/brain barrier and elicit pro-cognitive effects in recognition and spatial learning and memory tasks in rats (Table **4**).

Interestingly, Carlini *et al*. [101] showed that intra-hippocampal ghrelin administration prior the training session, but not prior the test session (performed 24 h after training), improved the long-term memory of rats in the step-down inhibitory avoidance task (Table **4**). These findings suggest that ghrelin modulates molecular and/or cellular signaling events involved in memory acquisition and/or consolidation, but not in memory retrieval [101]. Moreover, recent electrophysiological studies provided evidence showing that *in vivo* ghrelin microinjection into the CA1 subregion of hippocampus of rats reduced the threshold values to generate LTP in the dentate gyrus, which is the first synaptic input arising the hippocampus from entorrinal cortex. Moreover, a significant negative correlation was established between this electrophysiological phenomena and the ghrelin effect on the step-down inhibitory avoidance task [102] (Table **4**).

In relation to the signaling pathway, it was demonstrated that ghrelin increases nitric oxide synthase (NOS) activity in a dose-dependent manner in trained animals, suggesting the participation of the NOS/NO pathway in the ghrelin's effects on memory [102]. Moreover, it has been also postulated that GHS-R1a likely serves as a modifier of key neurotransmitters required for memory formation such as glutamate, dopamine and serotonin [104]. For instance, Albarran- Zeckler and co-workers [104] demonstrated that genetic deletion of GHS-R1a has opposing regulatory effects on learning and memory. While spatial memory was improved in the *ghsr*$^{-/-}$ mice, contextual memory was impaired by the lack of this receptor (Table **4**). One plausible explanation for these results is that ghrelin acts as a neuromodulator of other neurotransmitters such as dopamine. Of particular relevance, studies have shown that antagonism of dopamine D1 receptors in the hippocampus blocks formation of long-term memory [105] and dopamine D1 receptor knockout mice show deficits in contextual fear conditioning [106]. Interestingly, it was recently demonstrated by the Smith's group (The Scripps Research Institute, Florida, USA) that the ghrelin receptor (GHS-R1a) is co-expressed in neurons that express dopamine D1 and D2 receptors, and that a subset of GHS-R1a, which are not occupied by the agonist (apo-GHS-R1a), heterodimerize with these two receptors to regulate dopamine-induced feeding suppression in mice [107]. It is thus very likely that there is similar importance of the GHS-R1a for effects of dopamine signaling on learning and memory.

In addition, it was demonstrated that the selective serotonin reuptake inhibitor (SSRI) fluoxetine, given i.p. 30 min prior to intra-hippocampal ghrelin injection, prevented the ghrelin-induced increase in food intake and short- and long-term memory retention in rats [99]. These findings suggest that the effects of ghrelin on both feeding and memory retention could depend on the availability of serotonin. Experiments using hipocampal slices demonstrated that few minutes after addition of ghrelin in the superfusion medium, serotonin release was inhibited [108]. In another set of experiments, ghrelin was injected into the hippocampus of rats and the animals were killed 24 h later for the measurement of serotonin release. Remarkably, ghrelin significantly inhibited the serotonin release 24 h after its *in vivo* administration, indicating that ghrelin-induced inhibitory effects on serotonin release starts immediately after injection and can persist for at least 24 h after its central administration [108].

Certainly additional brain systems and molecular mechanisms need to be studied to further clarify the role of ghrelin on learning and memory processes. However, from recent findings demonstrating the ability of ghrelin to improve the cognitive dysfunction in rats submitted to models of sepsis-associated encephalopathy [109] and diabetic encephalopathy [110], it appears that ghrelin might be particularly useful to restore impaired learning and memory processes associated to neurodegenerative diseases.

GHRELIN AS A PALLIATIVE TREATMENT FOR DEPRESSION IN NEURODEGENERATIVE DISEASES

Depression is a prevalent disease; 10-20% of people in the world's population will develop depression at least once in their lifetime, causing impairment in functioning and quality of life, with high medical and social costs [111,112]. According to World Health Organization major depression will be the world's second most debilitating disease by 2020, eclipsed only by heart disease [113]. This disease is characterized by apathy, indifference and anhedonia, behavioral sluggishness and increasing inactivity, feelings of guilt, pessimism, regret and low self-esteem, psychophysiological disturbances of sleep and appetite [111]. Major depression is frequently found coexisting with long-standing chronic medical conditions such as cardiovascular disease, diabetes mellitus, obesity and neurodegenerative diseases [114].

Depression is common and a clinically important feature of PD and can precede the onset of the motor symptoms. The prevalence of depression in patients with PD is approximately 40% [115,116]. Concomitant depression in PD is associated with greater healthcare system use, including medical hospitalizations [117]. Moreover, major depressive disorder is considered a risk factor for developing AD later in life [118]. Depressive symptoms are frequent and affect nearly 40% of AD patients [119]. Noteworthy, brains of patients with AD with comorbid depression showed higher levels of cortical neurofibrillary tangles than brains of patients with AD without comorbid depression, suggesting an interaction between depression and the neuropathologic processes in AD [120].

Drugs used in the treatment of depression cause several side effects and generally influence weight gain. Among hormones that act on weight regulation, ghrelin has been suggested to exert an antidepressant action. Regarding the preclinical studies, there are several pieces of evidence supporting a role for ghrelin in the modulation of mood (Table **5**). The administration of antisense DNA for ghrelin into the lateral ventricle was reported to reduce the immobility time in the forced swimming test (FST) in rats, which is a result indicative of an antidepressant-like effect [121]. Further evidence of the possible antidepressant activity of ghrelin, it is a study by Lutter *et al*. [122] showing that the subcutaneous administration of ghrelin produced antidepressant-like responses in the FST. In addition, increasing ghrelin levels through a diet containing 60% of normal calories resulted in an antidepressant-like response in the FST. Moreover, mice submitted to chronic social defeat stress (CSDS) procedure, which induces behavioral deficits reminiscent of depression including social avoidance, had significantly elevated levels of acylated ghrelin that persisted for at least 4 weeks after the procedure [122]. Moreover, genetic deletion of GHSRs exacerbated depression-like behavior induced by CSDS, a finding also described by Chuang *et al.* [123]. The study by Lutter *et al.* [122] demonstrated that ghrelin's antidepressant-like effects in the FST were blocked in mice lacking orexin, suggesting that the antidepressant-like actions of this peptide may be dependent on a direct and/or indirect activation of orexin-containing neurons.

A recent evidence provided by our group [124] reinforced the notion of the ghrelin's antidepressant action, since it was shown

Table 5. Summary of the Ghrelin's Antidepressant-Like Effects Observed in Preclinical Studies.

Animal Model	Main Findings	References
Forced swimming test	Antidepressant-like effect following the administration of antisense DNA for ghrelin into the lateral ventricle, or subcutaneous administration of ghrelin in rats. Also, increasing ghrelin levels through a diet containing 60% of normal calories caused antidepressant profile. Antidepressant-like effects of ghrelin in the FST were blocked in mice lacking orexin	[122]
Tail suspension test	Acute administration of ghrelin by i.c.v. route caused antidepressant-like effect in mice	[124]
Olfactory bulbectomy	Acute administration of ghrelin by i.c.v. route abolished the depressive-like behavior induced by olfactory bulbectomy in mice	[124]
Chronic social defeat stress (CSDS)	Genetic deletion of GHSR exacerbated depression-like behaviors induced by CSDS	[122,123]

that the acute administration of ghrelin by i.c.v. route produced antidepressant-like effect in a predictive test of antidepressant activity, the tail suspension test (TST) in mice. In addition, this study also showed that ghrelin, administered acutely to mice by i.c.v. route, was able to abolish the depressive-like behavior induced by olfactory bulbectomy (OB) [124], an animal model of depression which produces behavioral, neurochemical and neuroendocrinological changes that resemble some of the symptoms observed in depressed patients [125]. Of note, these behavioral and neurochemical changes in OB rodents are reported to be normalized only by the chronic administration of antidepressants. Interestingly, there are few studies reporting that the acute administration of agents that inhibit the glutamatergic transmission such as zinc and riluzole produce a rapid reversal of the hyperlocomotion activity induced by OB [126,127], as opposed to the conventional antidepressants. Therefore, it remains to be established if an antiglutamatergic mechanism could be responsible for the antidepressant-like effect of ghrelin.

Clinical studies have also supported the idea that ghrelin exerts a possible beneficial role in depressive disorders. The serum ghrelin levels were lower before and after treatment in depressive patients as compared with non-depressed individuals [128,129]. Moreover, it was demonstrated that electroconvulsive therapy (ECT), an effective treatment for depression, decreased serum ghrelin levels in depressive patients as compared with the levels of this peptide before ECT [130]. Taking into account that ghrelin inhibits serotonin release [108,131], one of the hypothesis raised to explain these results is that the decreased circulating ghrelin levels may be a compensatory response to depression, potentially elevating serotonin levels [129]. Moreover, after a pulsatile administration of ghrelin to depressive patients, an improvement in the depressive symptoms assessed by a validated self-rating scale ('Befindlichkeits-Skala'), at trend level ($p=0.093$) in men, but not in women, was observed [132]. Furthermore, ghrelin gene polymorphism was previously associated with depression [133]. However, is must be conceded that other studies failed to show a correlation between ghrelin and depression [134,135]. For instance, nocturnal plasma ghrelin of depressed patients and matched healthy subjects did not differ when stratified for sex [134] and plasma ghrelin was not different between 83 depressed patients and 46 healthy controls [135].

Several studies have linked ghrelin with stress, which, in turn, is a risk factor for the development of depression. Humans subjected acutely to psychosocial stress exhibit increased plasma ghrelin levels [136], and similar results were described in rats after acute psychological stress [137]. The increase in ghrelin levels could contribute to the mechanisms responsible for the development of stress-induced depression or may represent a protective mechanism to minimize manifestations of depression following stress [37,138,139]. This protective mechanism may be related to the activation of hedonic signalling pathway and stimulation of the intake of palatable caloric foods that, in turn, elicits central reward pathways and increases dopamine signaling [139]. However, the stress-induced food rewards behavior and hyperphagia of palatable caloric dense foods increases body weight. Following prolonged exposure to stress and palatable foods, a desensitization of reward signalling may be linked to the risk of depression and co-morbid obesity [139].

Another possible mechanism that links ghrelin to depressive disorders is that a ghrelin's action on mood may be mediated through the modulation of neuroinflammatory mechanisms [138], which has been demonstrated to play a role in the pathophysiology of depression [114,140,141]. Therefore, it remains to be established if ghrelin administration is able to ameliorate the depressive-like behavior elicited by neuroinflammatory conditions in rodents, taking into account that ghrelin or ghrelin mimetics are able to suppress the synthesis and release of pro-inflammatory cytokines [142].

GHRELIN AS A PALLIATIVE TREATMENT FOR Of Stress And Anxiety Disorders IN NEURODEGENERATIVE DISEASES

The gut-brain connection has been implicated in brain disorders ranging from anxiety to depression and schizophrenia [143-145]. This connection between gastrointestinal tract and the hypothalamic-pituitary axis (HPA) is bidirectional and it is mediated through the release of peptides that exert responses within the brain as well as via neuroendocrine and sensory inputs from the gut. The exact mechanisms governing such communication are unclear and most studies focus on the impact of altered signaling from the brain to the gut although the reverse is now being studied (for review see [144,145]). Even though a complete discussion of the interrelationships between the gut and the brain in the control of stress and anxiety disorders is beyond the intended scope of this article, focus will be placed on briefly reviewing the current literature on ghrelin and its role in the mediation/modulation of stress/anxiety states.

There is increasing evidence that ghrelin has several physiological functions, especially in CNS, including a role in neuroprotection, learning and memory, reward and motivation, and depression as aforementioned, besides being important in anxiety and stressful conditions (for review see [37]), since plasmatic ghrelin is able to cross the blood–brain barrier, and to accumulate and bind to neurons in several brain areas underlying stress and anxiety responses. Actually, the orexigenic and pro-obesity targets of ghrelin's actions are located in hypothalamic and mesolimbic circuits involved not only in energy balance, appetite and reward but also in regulating mood and cognition (for review see [146]).

Animal and human studies suggest that stressful conditions can result in low mood and increased energy intake, particularly from fatty acids and sugars, and potential changes in body weight, leading to obesity. These effects involve changes in neuroendocrine and peripheral metabolic substrates which alter feeding behavior [147]. Although it is well known the function of cortisol/corticosterone, as well as the role of HPA axis, in the stress-induced eating of caloric "comfort foods", the molecular substrates and neuronal circuits controlling the complex behaviors responsible for these processes remain mostly unknown. However, one aspect has been established in recent years: stress-induced food reward is dependent on signaling by ghrelin [123], among other neuropeptides [148]. In view of the fact that stress-induced food reward is dependent on ghrelin [149], it is conceivable that ghrelin could be involved in the underlying mechanisms of stress responses and, therefore, of anxiety states.

Stress is known to modify circulating ghrelin and also ghrelin-O-acyltransferase (GOAT) levels with differential responses related to the type of stressors, including a reduction of ghrelin induced by physical stressors (abdominal surgery and immunological/endotoxin injection, exercise) and an elevation by metabolic (cold exposure, acute fasting and caloric restriction) and psychological stressors, which may contribute to the neuroendocrine and behavioral responses besides the energy requirement needed after repeated exposure to stressors (for review see [150]). Circulating levels of ghrelin are high during fasting in several species including man [151] and it is also increased by stressors, such as tail pinch [152], water immersion [153], social defeat [122], restraint stress [154] and chronic stress (caged filled with water) [155]. Of high importance, behavioral studies performed by independent research groups have shown that centrally administered ghrelin also participates in the expression of anxiety-like behavior in rodents (Table **6**).

Central or systemic administration of ghrelin promotes anxiogenic-like behavior in both rats and mice [95,96,152], as evaluated in the elevated plus maze and other behavioral tests. Ghrelin also promotes anxiogenesis in chicks evaluated in an open-field [159]. Moreover, ghrelin antisense oligonucleotides produced an anxiolytic-like effects in the elevated plus maze, black and white, and conditioned fear tests in rats [121]. These anxiogenic-like effects of ghrelin were inhibited by administration of a corticotropin-releasing hormone receptor antagonist [152]. Thus, they are probably due to the activation of paraventricular nucleus (PVN) where GHS-R1a mRNA is expressed at high levels [160], supporting the hypothesis of a direct activation of GHS-R1a on CRH-containing neurons. Ghrelin administration also stimulates adenocorticotropic hormone (ACTH) cell hypertrophy and proliferation, and promotes ACTH and corticosterone/cortisol release in several species including humans [152,161,162]. Taken together, these findings suggest that ghrelin levels increases in response to psychological stress and that ghrelin may influence behavioral and neuroendocrine responses to stressors, possibly via the mobilization of ACTH. Furthermore, the stress-induced increase in plasma ghrelin was associated with the acute response of serum cortisol to stress [136].

Ghrelin also controls anxiety-like behavior through the serotonergic system, since administration of ghrelin in specific rat brain regions showed that ghrelin promotes a more prominent anxiogenic-like behavior when injected into the dorsal raphe nuclei (DRN) [96], the primary site of serotonergic neurons in the brain, and this effect seems to be mediated by an inhibition of serotonin release. Actually, ghrelin appears to have an impact on the HPA

Table 6. Summary of the Ghrelin's Effects on Anxiety-Like Behavior Observed in Preclinical Studies.

Animal Model	Main Findings	Reference
Elevated plus maze Open field Black and white box Social interaction	Increased anxiety-like behavior in ghrelin-treated rats	[156]
Elevated plus-maze Open-field	Anxiogenic-like effect in rats after central injection of ghrelin	[95]
Elevated plus-maze Black and white box Conditioned fear	Antisense oligonucleotides of ghrelin produced an anxiolytic-like effect in rats	[121]
Elevated plus-maze	Ghrelin promoted a more prominent anxiogenic-like behavior when injected into the dorsal raphe nuclei (DRN) in rats	[96]
Elevated plus-maze Open-field Light/dark box	Ghrelin knockout mice were more anxious than wild type mice after an acute restraint stress	[157]
Elevated plus-maze	Rats injected into the arcuate nucleus or paraventricular nucleus with ghrelin showed an anxiogenic-like behavior	[158]
Elevated-plus-maze	Anxiogenic-like effect in mic after intracerebroventricuar and intraperitoneal administration of ghrelin	[152]
Elevated plus-maze	Acute administration of ghrelin promoted an anxiolytic-like responses in mice	[122]
Open-field	Anxiogenesis in chicks	[159]

response via a serotonergic pathway [163]. In this regard, 80% of DRN neurons were classified as putative serotonin-containing neurons and ghrelin depolarized 75% of them [164]. Ghersi *et al*. [108] also showed that ghrelin inhibited serotonin release in hippocampal slices. A chronic (4 weeks) central exposure to ghrelin promoted an increase in anxiety- and depression-like behavior in rats. Changes in expression of a number of genes representing key systems implicated in these behavioral effects were found as well as an inhibition of the electrophysiological response of DRN after a ghrelin challenge [156].

Additionally, anxiogenic and orexigenic effects of ghrelin seems to be mediated, at least in part, via endocannabinoid signaling since PVN injections of the ghrelin promoted anxiogenic-like profile and a significantly increase in food intake and these effects were blocked by AM251, a cannabinoid CB1 receptor antagonist [158].

On the other hand, caloric restriction for 10 days or acute administration of ghrelin promoted an increase in circulating ghrelin levels in *ad libitum*-fed C57BL6/J mice, producing anxiolytic-like responses in the elevated plus maze. However, when GHSR-null mice were calorie-restricted, these anxiolytic-like behavioral responses were no longer observed indicating a specific role of GHS-R1a receptors in this effect [122]. In addition, recently, it was shown that ghrelin knockout mice are more anxious after an acute restraint stress, compared with wild-type mice, as evaluated in three behavioral tests (elevated plus-maze, open-field and light/dark box). Acute restraint stress exacerbated neuronal activation in the hypothalamic PVN and medial nucleus of the amygdala in knockout mice compared with wild type mice, and the administration of exogenous ghrelin was able to reverse this effect. Spencer *et al*. [157] proposed that ghrelin is able to reduce anxiety after acute stress by stimulating the HPA axis at the anterior pituitary level, by involving urocortin 1 receptor on this effect. These observations showing an anxiolytic-like effect of ghrelin seem to be supported by findings that ghrelin levels were higher in the Sprague–Dawley rats (low-anxiety strain) than in the Wistar Kyoto rats (high-anxiety strain) after acute stress, whereas ACTH are equally enhanced in both strains [137,165]. Moreover, although psychological stress induces an increase in plasma ghrelin levels in humans, the post-stress induced urge for uncontrolled eating is not acutely modulated by stress related elevations in ghrelin levels [136]. In this regard, a recent study described that isolation stress resulted in a reduction of plasma ghrelin that seems to be dependent on CRF1-R, and MC4 receptor in PVN and 5-HT1B/2C receptors in the arcuate nucleus (ARN) [166]. The number of immunoreactive neurons in PVN of the hypothalamus was significantly increased after peripheral administration of ghrelin, an effect that seems to occur via NPY-positive projections from the ARN [167]. As the PVN is involved in a neuronal network mediating the autonomic, neuroendocrine, and skeletal-motor responses of fear and anxiety [168], an increased density of immunoreactive neurons in the PVN, after peripheral ghrelin administration, could also be the result of ghrelin transport into the brain and/or resultant of an activation of the hippocampal–amygdalic–hypothalamic network involved in the regulation of fear and anxiety rather than an activation of hunger/satiety pathways along the ARN-PVN axis [167]. In addition, rates of anxiety and cognitive impairment were higher in the hypertensive elders, which were negatively correlated with plasma ghrelin levels, resulted from chronic cortisol response to long-term anxiety [169].

The reason for these contradictory findings are presently unknown, but it could be related in animals to the timing of the behavioral tests after ghrelin administration since the anxiogenic-like effect of ghrelin was seen when the behavioral evaluation was performed within 5-10 min [95,96,121,152,158], whereas the latter study conducted the evaluation after 45 min of the injection [122]. As ghrelin has a plasmatic half-life of about 30 min, it is conceivable that the dose which had significant effects on food intake in all previous studies, underlined the anxiogenic responses in the 5-10 min studies. These issues have to be clarified since not all studies show changes in ghrelin levels [134,135].

Several findings suggest that ghrelin was secreted as a result of alarm signals concerning physiological changes such as severe weight loss, which are potentially life threatening [155]. Altogether, evidence shows that ghrelin is involved in emotional reactivity in rodents, although no differences were found in patients with obsessive compulsive disorder [170]. Thus, ghrelin is a peptide hormone implicated in diverse biological functions such as the modulation of centrally controlled behaviors ranging from energy balance (food intake, body-weight regulation and glucose homeostasis) to stress, anxiety and memory processes. Some regions of the hypothalamus appear to be differentially sensitive and responsive to the feeding-stimulant, metabolic, and anxiogenic actions of ghrelin and that the ARN and PVN, in particular, exert a primary role in mediating these effects [158].

Therefore, the bidirectional effects of ghrelin on stress and anxiety behaviors seem to be stressor, test- and time-dependent, and may be partly mediated by ghrelin via the CRF, serotonin and the endocanabinoid systems.

CONCLUSION

This article reviews the recent evidence that the gastric hormone ghrelin plays an important role not only as a modulator of GH secretion and food intake, but fundamentally as an important factor for neuronal plasticity, growth and survival in the CNS. Possible therapeutic opportunities for neurological disorders through the modulation of ghrelin system are pointed out, in the expectancy that this review may inspire clinical researchers and foster experimental approaches using ghrelin as the therapeutic target.

Two major conclusions should be drawn: first, the physiological role of ghrelin is by far wider than considered before including learning and memory, anxiety, depression and neuroprotection; second, changes in the GHS-R1a receptors seem to underlie these central actions of ghrelin. Establishing the function of ghrelin in physiological stress responses and whether control of its activity would be useful for prevention and/or treatment of stress-induced diseases, such as anxiety and mood disorders as well as psychiatric symptoms associated to neurodegenerative diseases, remain important research aims.

Since apoptotic cell death, mitochondrial dysfunction, oxidative stress and neuroinflammation have been identified as molecular processes associated with the neurological disorders here presented, manipulation of the ghrelin system beckons as an opportunity for neuroprotection, improving neuronal plasticity and counteracting the lost of brain functions in patients with neurodegenerative diseases, including AD and PD. Future research aiming the development of novel non-peptide ghrelin receptor antagonists, a growing number of ghrelin receptor selective ligands, and also inverse agonists, will help to elucidate the neurobiology and physiological role of ghrelin as well as its potential as novel palliative and neuroprotective agent in neurodegenerative diseases.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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