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Review

Ghrelin: A link between ageing, metabolism and neurodegenerative disorders

I.I. Stoyanova *

Biomedical Signals and Systems, Faculty of Electrical Engineering, Mathematics and Computer Sciences, Institute for Biomedical Engineering and Technical Medicine MIRA, University of Twente, Enschede, The Netherlands

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ABSTRACT

Along with the increase in life expectancy over the last century comes the increased risk for development of age-related disorders, including metabolic and neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases. These chronic disorders share two main characteristics: 1) neuronal loss in motor, sensory or cognitive systems, leading to cognitive and motor decline; and 2) a strong correlation between metabolic changes and neurodegeneration. In order to treat them, a better understanding of their complexity is required: it is necessary to interpret the neuronal damage in light of the metabolic changes, and to find the disrupted link between the peripheral organs governing energy metabolism and the CNS. This review is an attempt to present ghrelin as part of molecular regulatory interface between energy metabolism, neuroendocrine and neurodegenerative processes. Ghrelin takes part in lipid and glucose metabolism, in higher brain functions such as sleep–wake state, learning and memory consolidation; it influences mitochondrial respiration and shows neuroprotective effect. All these make ghrelin an attractive target for development of biomarkers or therapeutics for prevention or treatment of disorders, in which cell protection and recruitment of new neurons or synapses are needed.

Contents

* EWI, BSS, University of Twente, PO Box 217, 7500 AE Enschede, The Netherlands. Fax: +31 53 489 2287.
E-mail address: stoyanovai@yahoo.co.uk.
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Introduction

Ageing and related disorders

Improvements in life style and public health care have led to a significant increase in average lifespan over the last century (Vaupel, 2010). Along with this comes increased risk for development of age-related disorders including neurodegenerative diseases (NDD). Ageing is a highly complex process determined by genetic and environmental factors. Changes in life style such as a moderate caloric restriction might slow ageing, reduce age-related chronic diseases (Pitsikas and Algeri, 1992), improve some metabolic markers of ageing and even extend the life span (Weindruch and Walford, 1988).

Brain ageing is accompanied by metabolic, morphological and neurophysiological changes, particularly associated with impairments in learning and memory (Rosenzweig and Barnes, 2003). There are gender differences in brain ageing e.g., brain atrophy starts earlier in men however, the progression is more rapid in women (Takeda and Matsuzawa, 1985). There is a loss of synapses, decrease in N-Methyl-D-aspartate (NMDA) receptor responses, and alterations in calcium homeostasis predominantly in regions essential to cognitive function (Fontán-Lozano et al., 2007). Thus ageing impairs synaptic plasticity, which is a basis for memory (Gruart et al., 2006), and changes the long-term potentiation (LTP), regarded as a mechanism underlying learning (Banks et al., 2014).

Chronic NDD which include Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) diseases are progressive, associated with high morbidity and mortality because, so far, there are very limited to no options for their treatment. Although different, NDD share two important characteristics: first, systemic loss of neurons in motor, sensory or cognitive systems (Martin, 1999) leading to cognitive and motor decline; and second, a correlation between metabolic changes and neurodegeneration (Cai et al., 2012). The regenerative ability of neuronal tissue is limited therefore, it is important to restrict neuronal impairment and death. The processes in NDD are quite complex, and it is of primary significance to interpret the neuronal damage in light of the metabolic changes, and to look for disrupted connection between the peripheral organs governing the energy metabolism and CNS, i.e. for alterations in the signalling molecules.

Ageing and the associated disorders involve perturbed energy balance. Metabolism is regulated by both central inputs (mainly hypothalamic) and peripheral signalling molecules such as insulin, ghrelin, cholecystokinin, and adipokines (leptin, adiponectin, resistin). On the other hand, one of those molecules — ghrelin, has also remarkably wide and complex spectrum of effects on the neurons. Therefore, this review is attempting to present ghrelin as a link between metabolism, influenced by some life style aspects such as diets and sleep, and the pathogenesis of neurodegeneration, and to emphasise on its potential for creating biomarkers or therapeutics for management of metabolic and NDD.

Ghrelin

Synthesis and functions

Ghrelin is a 28-amino acid peptide, growth hormone (GH) secretagogue (GHS) and appetite stimulator (Kojima et al., 1999). Ghrelin is produced mainly by gastric oxyntic cells (Date et al., 2000). They have no contact with the glandular lumen; rather they are closely associated with capillaries, suggesting an endocrine role of ghrelin (Camiña et al., 2003). There is a second type of ghrelin-producing cells in the remainder of the gastrointestinal tract (GIT) which are in contact with the intestinal lumen (Sakata et al., 2002). These two types of cells may be distinctly regulated and play different physiological roles. Ghrelin production has also been attributed to the pancreas (Date et al., 2002b; Wierup et al., 2002).

Ghrelin has been detected within the brain: in neurons of the hypothalamic arcuate nucleus (ARC) (Kojima et al., 1999), ventromedial hypothalamic nucleus (VMN) and paraventricular nucleus (PVN) — areas related to the control of GH-secretion and the appetite (Cowley et al., 2003). Ghrelin-immunoreactive (IR) neurons have been observed in the internuclear space between the lateral hypothalamus (LH), ARC, PVN, VMN and dorsomedial nuclei and the third ventricle which highlights a different central role for ghrelin. Their location overlaps the area with hypothalamic projections from the suprachiasmatic nucleus (SCN), where the circadian clock resides and from the ventral lateral geniculate body (Horvath, 1997, 1998). Thus, the central ghrelin expression determines a conjunction of the daily rhythms with visual stimuli (Cowley et al., 2003) in accordance with ghrelin's meal-initiating effect (Cummings et al., 2001).

Ghrelin-IR neurons have also been found outside the hypothalamus, in the sensory-motor cortex and the cingulated gyrus (Hou et al., 2006). In the primary sensory cortex they are much more in neonates than in adult rats (Stoyanova, 2012; Stoyanova et al., 2009) suggesting a possible role during the early postnatal formation and remodeling of the brain cortex.

Ghrelin gene encoded first preproghrelin, which is cleaved to proghrelin. Proghrelin is further cleaved to produce unacylated ghrelin (des-acyl ghrelin or DAG) and acylated ghrelin (AG, C-ghrelin, or also referred to as ghrelin) (Hosoda et al., 2000). AG represents 10% of the total circulating ghrelin (Ariyasu et al., 2001). It exerts central and peripheral effects via GHS-receptor-1a (GHSR1a), a G protein-coupled receptor (Kojima et al., 1999). AG binds to GHSR1a when caprylic (octanoylic) acid is linked to serine by the enzyme ghrelin-O-acyltransferase (GOAT) (Yang et al., 2008). The *n*-octanoyl group seems to be essential for its binding and for some of AG effects (Van der Lely, 2009). AG has metabolic and endocrine effects: induces food intake and accelerates gastric emptying (Inhoff et al., 2008) via acetylcholine system (Date et al., 2001). AG increases GH, prolactin, adrenocorticotropic hormone (ACTH), and cortisol levels. It inhibits insulin and PP secretion and increases plasma glucose levels (Kumar et al., 2010). These endocrine actions are not mediated by the cholinergic system (Broglio et al., 2003). AG levels are elevated in obesity and type 2 diabetes mellitus (DM) (Rodriguez et al., 2009). Insulin-resistant obese subjects have higher AG/DAG ratio, suggesting that AG excess can contribute to obesity-associated insulin resistance (Barazzoni et al., 2007).

DAG is an unmodified (unacylated) form of ghrelin, dominant in the plasma (90%) (Ariyasu et al., 2001). Until recently, DAG was considered as inactive because it does not bind to GHSR1a (Kojima et al., 1999). However, DAG participates in many physiological and pathological processes (Thompson et al., 2004), suggested to be considered as a separate hormone, acting independently or together with AG (Broglio et al., 2004; Delhanty et al., 2014). DAG is lower in obesity whereas AG levels are unchanged indicating that DAG might be regulated by body weight (Pacifico et al., 2009).

DAG induces negative energy balance increasing postprandial insulin and decreasing AG, improves insulin sensitivity and decreases fat mass (Asakawa et al., 2005; Benso et al., 2012). These effects are acute and, at least partly, orchestrated in the hypothalamus (Martens et al., 2010). In GHSR1a-deficient mice DAG modulates the expression of metabolically important genes (Delhanty et al., 2010). Administration of GHSR1a-blockers antagonizes the AG effect on insulin secretion whilst they do not affect DAG-induced insulin output which indicates the existence of a specific DAG receptor (Gauna et al., 2006). The correlation between DAG effect on postprandial glycaemia and the preprandial AG levels makes DAG clinically relevant in subjects with relatively high AG levels (Delhanty et al., 2012).

AG and DAG interact, and depending on the experimental setup, DAG can either antagonize or support AG (Delhanty et al., 2012). Administration of AG in GH-deficient patients induces rapid rise in insulin and glucose levels, reducing insulin sensitivity, whereas the combination of AG and DAG strongly improves insulin sensitivity (Gauna et al.,

2004). AG suppresses PP secretion but it is counteracted by coadministration of DAG (Kumar et al., 2010). DAG together with AG diminishes insulin and glucose response to AG, whilst DAG administration alone had no effect (Broglio et al., 2004). These findings indicate that DAG can be metabolically active by abrogating the effect of AG on insulin secretion and glucose metabolism.

Secretion and associated disorders

Ghrelin secretion is regulated by nutritional and hormonal factors (Rigamonti et al., 2002). Fasting and a low-protein diet increase ghrelin-mRNA expression and plasma ghrelin, whilst there is a postprandial ghrelin decrease (Lee et al., 2002b). The temporal patterns of ghrelin release are reciprocal to insulin but in a phase with leptin: ghrelin and leptin decrease after meals (Cummings et al., 2001). Meals inhibit secretion of both AG and DAG, whereas long-term fasting inhibits acylation but not total secretion (Lucidi et al., 2004). Acylation may be regulated independently of secretion by nutrient availability in the gut or by esterases cleaving the acyl group (Liu et al., 2008).

Sleep deprivation has been linked with increased ghrelin (Bodosi et al., 2004). In healthy humans, total ghrelin shows an initial nocturnal elevation and declining towards the morning (Spiegel et al., 2011). The significance of it remains unknown, and data provided by different studies are inconsistent. AG/DAG ratio is lower during sleep, suggesting that GOAT activity may decrease during sleep. Thus, sleep has an inhibitory effect on AG (Spiegel et al., 2011). The elevated nocturnal DAG could be a result of increased vagal tone (Date et al., 2001). In night workers and people with impaired sleep nocturnal ghrelin is increased but combined with blunted postprandial suppression (Schiavo-Cardozo et al., 2013). Nocturnal ghrelin increase is blunted in obese subjects (Dzaja et al., 2004) but markedly elevated in anorexia nervosa (Müller et al., 1995). However, a partial weight recovery brings it back to normal (Otto et al., 2001) possibly because of ghrelin resistance in cachexia (Camiña et al., 2003).

Somatostatin, leptin, insulin, insulin-like growth factor-I (IGF-I), high-fat diet (Shimada et al., 2003) and obesity (Tschöp et al., 2001) inhibit ghrelin production. Because fasting ghrelin is negatively correlated with insulin and leptin, the lowered ghrelin may be a consequence of elevated insulin or leptin, a mechanism regarded as a physiological adaptation to the positive energy balance of obesity (Ravussin et al., 2001). Ghrelin is downregulated with ageing. In elderly healthy normal weight people the values are as low as those in young obese, and significantly lower than those of young non-obese subjects (Rigamonti et al., 2002). However, is this decrease due to ageing per se or is it a consequence of age-related changes in other factors regulating ghrelin synthesis and release, is not fully determined.

Ghrelin and gastrointestinal control and energy metabolism

Ghrelin has effects on food intake, gastrointestinal function and energy. Food intake is controlled by a central homeostatic mechanism triggered by satiety and starvation signals from the gut. Gut hormones not only influence brain but also are expressed in there in concentrations higher than those in the intestine (Dockray, 1976). This and the widespread expression of their receptors by neurons raised the prospect of cross-talk between gut and CNS. The effects of gut hormones on CNS neurons are either direct or mediated by vagal afferents (Davison, 1986). Several hormones, such as cholecystokinin, leptin, glucagon-like peptide-1 (GLP-1), and peptide $YY_{3–36}$, stimulate vagal afferents and activate the pathway leading to inhibition of food intake and gastric emptying (Dockray, 1988). However, there are other signalling molecules with opposite (orexigenic) effect. Ghrelin (Date et al., 2002a; Kojima et al., 1999), orexin-A (Burdyga et al., 2003) and endocannabinoids (Gomez et al., 2002) stimulate feeding and accelerate gastric emptying. Subdiaphragmatic vagotomy or capsaicin treatment completely abolishes feeding and GH response to ghrelin, indicating that these effects are mediated by the vagal nerve (Date, 2012). The interactions between satiety and orexigenic signals are of significance for the control of digestion, therefore, their understanding is of great importance, particularly in respect to the worldwide increase in obesity and for development of potential non-invasive approaches for its treatment. The complexity of the dialogue between the gut and the brain was presented in an elegant way by Dockray (2014).

Ghrelin's orexigenic signals from the gut are transmitted to neurons located in the ARC via the bloodstream (Hewson and Dickson, 2000) or to the nucleus of the solitary tract (NTS) via the vagal afferents (Date, 2012). Within the ARC, there are orexigenic neurons expressing neuropeptide Y (NPY) and agouti-related protein (AgRP) (Hahn et al., 1998), and anorexigenic neurons expressing pro-opiomelanocortin (POMC), α-melanocyte stimulating hormone (α-MSH) and cocaine- and amphetamine-regulated transcript (CART) (Andrews, 2011; Zheng et al., 2003). AgRP was detected in 94% of NPY neurons (Hahn et al., 1998) and their activation initiates feeding (Cummings et al., 2001). The presence of GHSR1 in 94% of NPY neurons (Willesen et al., 1999) along with the fact that 90% of NPY cells are activated by intraperitoneal ghrelin application suggests a direct action of ghrelin on them (Wang et al., 2002).

Whilst ghrelin directly stimulates orexigenic AgRP/NPY activity, it indirectly inhibits anorexic POMC neurons via gamma-aminobutyric acid (GABA) input from the same AgRP/NPY neurons (Cowley et al., 2003). Deletion of vesicular GABA transporter in AgRP neurons eliminates the inhibitory input onto the postsynaptic POMC neurons leading to unopposed activation of the melanocortin system and anorexia (Tong et al., 2008). This GABA-mediated inhibition is accompanied by changes in POMC synaptic plasticity. Ghrelin increases the number of inhibitory synapses on POMC neurons, and thus elevates food intake by lowering anorexigenic signals (Andrews et al., 2008).

Hypothalamic feeding regulation dependent on internal energy status is referred to as homeostatic (Saper et al., 2002). However, there is another, hedonic feeding, triggered by external factors such as visual or olfactory food stimuli. Behavioural response to them involves the orbitofrontal cortex, amygdala, and striatum (Rolls, 1994), a part of the mesolimbic system implicated in reward and motivated behaviours (Cardinal et al., 2002). Intravenous ghrelin administration increases neuronal response to food pictures, demonstrating that ghrelin also favours food consumption by enhancing the hedonic and incentive responses to food-related cues (Malik et al., 2008).

GIT function

Gastric acid secretion is regulated by central and peripheral pathways via endocrine, neurocrine, and paracrine mechanisms. The central pathway is activated by sight, smell, taste and thought of food (Feldman and Richardson, 1986), whilst the peripheral pathway is triggered by mechanical and chemical stimuli (Lloyd and Debas, 1994). Most of the neurotransmitters orchestrating feeding behaviour also participate in the control of GIT function. Intraventricular ghrelin administration stimulates gastric acid secretion, an effect completely abolished by vagotomy or atropine administration (Date et al., 2001).

In addition to the peripheral ghrelin, there are hypothalamic ghrelinergic neurons projecting to the dorsal vagal complex (DVC) (Hou et al., 2006) which was also confirmed by in vivo extracellular recordings (Wang et al., 2007). Together with the expression of GHSR1 mRNA on the DVC neurons, it indicates that the effects of ghrelin on GIT function are mediated via the vagal nerve (Date et al., 2001). This may be physiologically relevant in preparing GIT to process food (Masuda et al., 2000).

Energy metabolism

Ghrelin also regulates glucose and lipid metabolism. Treatment of elderly or obese subjects with GHS induces hyperglycaemia and insulin

resistance, suggesting that ghrelin makes fine adjustment of insulin secretion and glucose metabolism (Muller et al., 2001). Interestingly, whilst intravenous administration of AG reduces insulin sensitivity, the combination of AG plus DAG strongly improves it (Gauna et al., 2004). AG targets the pancreatic islands directly and via a GH-dependent pathway (Delhanty and Van der Lely, 2011). Unlike AG, DAG induces negative energy balance (Asakawa et al., 2005). Peripherally administered DAG blocks the orexigenic effect of AG, improves insulin sensitivity and reduces fat mass (Zhang et al., 2008). Thus both acylated and nonacylated forms exert an acute and long-term control of glucose metabolism and insulin sensitivity, which could be clinically relevant (Van der Lely, 2009). AG increases adiposity GHSR1-independently (Tschöp et al., 2000), and inhibits lipolysis (Muccioli et al., 2004). Therefore, controlling AG/DAG ratio could help to regulate the balance between adipogenesis and lipolysis, and to prevent development of insulin resistance (Delhanty and Van der Lely, 2011).

The molecular mechanism of ghrelin activity links mitochondrial-mediated effects of G-protein coupled receptors on neuronal functions (Andrews, 2011). Ghrelin stimulates hypothalamic AMP-activated protein kinase (AMPK) (Andersson et al., 2004) which inhibits fatty acid biosynthesis, reduces hypothalamic concentration of malonyl-CoA, and consequently activates carnitine palmitoyltransferase-I (CPT1) (López et al., 2008). Activation of AMPK–CPT1 axis improves mitochondrial respiration and reduces the generation of reactive oxygen species (ROS) by uncoupling protein 2 (UCP2) which buffers excessive ROS (Andrews et al., 2005, 2008). Thus, ghrelin not only controls central and peripheral lipid metabolism (López et al., 2008), but via activation of the AMPK–CPT1–UCP2 pathway ghrelin maintains the bioenergetics capacity of AgRP/NPY neurons and increases their activity.

Ghrelin and higher brain functions

Ghrelin and sleep–wake state

The effects of ghrelin also concern the regulation of higher brain functions including sleep–wake state (Steiger, 2007). GHSR1- or ghrelin-knockout (KO) mice lack or have attenuated arousal responses to wake-inducing stimuli (Szentirmai et al., 2009). However, the effects of exogenous ghrelin are still not completely clear. Ghrelin microinjections into LH, medial preoptic area or PVN prior to the rest in nocturnal rodents increase wakefulness, motor activity and food intake, and suppress sleep. This “dark onset syndrome” occurs at the beginning of the active period and evidently ghrelin triggers it (Szentirmai et al., 2007). On the other hand, central administration of NPY (Szentirmai and Krueger, 2006) and orexin (Hagan et al., 1999) has the same effect. Because ghrelin-, orexin- and NPYergic neurons form a network (Cowley et al., 2003) with reciprocal interconnections, it could be speculated that the wake-promoting effect of ghrelin is due to stimulation of orexin- and NPYergic neurons (Szentirmai, 2012).

The effect on arousal differs between species and depends on the way ghrelin is applied. In rats, both systemic and central ghrelin injections stimulate wakefulness and suppress rapid-eye-movement (REM) and non-REM sleep (Szentirmai et al., 2007). In mice, intraventricular administration increases wakefulness and suppresses REM and non-REM sleep, and slow wave activity (SWA), whilst systemic ghrelin administration solely stimulates feeding but does not affect sleep–wake activity (Szentirmai, 2012). This could not be due to the fact that DAG only crosses the blood–brain barrier (Yagi et al., 2013) because ARC detects circulating ghrelin (Fry and Ferguson, 2010). These results indicate that circulating and brain-derived ghrelin does not activate the same central wake-promoting mechanism and the effects on wakefulness and feeding are independent from each other.

The effect of systemic ghrelin or GHSR1-agonist administration on sleep–wake activity is less consistent in the literature. In humans, the effect depends on age, gender and time of administration. Ghrelin does not modulate sleep in healthy women (Kluge et al., 2007b), but in depressed it diminishes the REM sleep (Steiger et al., 2011). In contrast, early in the night ghrelin induces sleep in young men but when injected at early morning there is no sleep-promoting effect and EEG remains unchanged (Kluge et al., 2007a). After intravenous ghrelin administration SWS and non-Rem sleep increase and wakefulness decreases in healthy men, however in women sleep-EEG remains unchanged (Kluge et al., 2007b, 2010). Since effects on sleep-EEG are absent in both the pre- and postmenopausal women, it is unlikely that estrogens contribute to this sexual dimorphism.

Ghrelin action during the night is dose-dependent: lower doses of ghrelin promote sleep in men but not in women (Steiger et al., 2011).

Ghrelin modulates the circadian system activity (Angeles-Castellanos et al., 2004). GHSR1 is expressed in SCN master clock (Zigman et al., 2006) and in brain regions activated in anticipation of scheduled meals. Ghrelin acts as a non-photic stimulus which alters timing of light-signalled behaviours and inhibits spontaneous locomotor activity. Ghrelin-KO and GHSR1-KO show greater activity when exposed to light for a long period (Lamont et al., 2014) which raises the question of how ghrelin could cause it. It is important that GHSR1 is expressed in other nuclei that are major inputs of the SCN master clock such as the paraventricular nucleus of the thalamus (PVT), supraventricular zone, dorsomedial nucleus of the hypothalamus (DMH) and LH. Therefore, the absence of receptor in GHSR1-KO may alter the effect of ghrelin on the outgoing signals from SCN (Leak and Moore, 2001). This hyperactivity in GHSR1-KO suggests that other brain areas such as PVT, the major circadian relay, may also be involved. Thus, the absence of ghrelin action in the PVT could potentially change the normal inhibitory effects of light on behaviour (Lamont et al., 2014). In GHSR1-KO the long-term exposure to light disrupts the synchrony among the SCN clock cells (Ohta et al., 2005) suggesting that there may be an interaction between the effects of light and ghrelin that extends beyond a simple deficit in the ability of GHSR1-KO to entrain to scheduled feeding (Lamont et al., 2014).

Ghrelin and memory

The hippocampus, amygdala and dorsal raphe nucleus (DRN) are involved in cognition. Ghrelin plays a role in it (Hansson et al., 2014) because their neurons express GHSR1 (Guan et al., 1997) and get activated by central ghrelin administration (Carlini et al., 2002). Their activity is considered as “high-order” feeding control because they are involved in the learning and motivation aspects of feeding (Kanoski et al., 2013). The dorsal hippocampus (DHPC) is associated with the control of learning/memory related to visuospatial processing (Fanselow and Dong, 2010), therefore ghrelin signalling in DHPC improves spatial memory performance (Chen et al., 2011). The ventral hippocampus (VHPC) is of importance in feeding and other appetitive/rewarding behaviours processing energy status-relevant neuroendocrine signals. Thus, VHPC ghrelin signalling increases the ability of environmental food-related cues to stimulate meal initiation and enhances the motivation to obtain it (Kanoski et al., 2013).

Intraamygdala AG injection influences learning and short-term memory, whilst the intra-hippocampal application improves the long-term memory only. These effects are GHSR1 mediated (Tóth et al., 2010). Ghrelin probably modulates specific intermediates involved in memory acquisition/consolidation, but not retrieval (Carlini et al., 2010) which could be related to serotonin (5-HT)-availability (Carlini et al., 2007). Association between 5-HT and learning/memory has been previously reported (Petkov and Kehayov, 1994), and 5-HT is considered as a prerequisite to maintain control over the cognition (Ghersi et al., 2011). Enhanced serotonin improves memory (Haider et al., 2006), whereas 5-HT depletion impairs it (Evers et al., 2005). Acute intraamygdala ghrelin administration increases activity of serotoninergic neurons projecting to it, whilst GHSR1-KO displays a decreased 5-HT activity (Patterson et al., 2010).

Ghrelin enhances synaptic plasticity and synaptogenesis. Peripheral ghrelin injections increase spine density in the hippocampus (Berrout and Isokawa, 2012), hypothalamus (Pinto et al., 2004) and the ventral tegmental area, important for motivational aspects of multiple behaviours (Abizaid et al., 2006). When chronically applied to cortical neurons, AG accelerates and prolongs synapse formation (Stoyanova et al., 2013), leads to earlier onset of activity, and generates "mature" activity pattern, and higher activity levels (Stoyanova and le Feber, 2014). These findings complement the in vivo obtained evidence, that elevated ghrelin during fasting enhances synaptic function NMDA-dependently (Fontán-Lozano et al., 2007). Ghrelin enhances memory task performances (Diano et al., 2006) and promotes the long-term potentiation (LTP) by elevation of nitric oxide synthase (NOS) activity (Carlini et al., 2008).

Metabolism, neurodegeneration, and ghrelin

Alzheimer's disease

AD is the most common NDD (Hebert et al., 2003) causing cortical and hippocampal neurodegeneration, which results in progressive cognitive and memory decline (West et al., 2000). Less than 1% of AD cases are genetically determined, and develop symptoms before the age of 65 (Cai et al., 2012), whilst the majority of cases are referred to as sporadic. Both forms express similar symptoms and pathophysiological mechanisms which involve mitochondrial alterations, membrane-associated oxidative stress, altered proteolytic processing of amyloid-beta (Aβ) precursor protein (APP) and accumulation of neurotoxic forms of Aβ-peptide (Mattson, 2004). The dynamics of AD biomarkers is very complex, they develop independently and in parallel, rather than as a cascade. The two major AD proteinopathies, Aβ and tau, might be initiated independently in sporadic AD, and Aβ pathophysiology can accelerate forerunning limbic and brainstem tauopathy (Jack et al., 2013).

Aβ and oxidative stress disrupt neuronal Ca^{2+}, thereby rendering neurons susceptive to excitotoxicity and the development of neurofibrillary tangles (NFTs) composed of hyperphosphorylated microtubule protein tau (Hardy et al., 1998). Memory deficits in AD correlate with the amount of Aβ deposited in the hippocampal neurons (Lefterov et al., 2009). In this respect, ghrelin might be a preventive strategy for amelioration of cognitive abilities because it has GHSR1-mediated neuroprotective effect against Aβ oligomer-induced toxicity (Moon et al., 2011). Ghrelin prevents ROS increase, calcium deregulation and mitochondrial dysfunction (Gomes et al., 2014).

Obesity and diabetes mellitus (DM) are associated with increased risk of developing dementia and AD (Moroz et al., 2008). DM shows AD-type neurodegeneration, therefore, the sporadic AD regarded to be as a brain type of DM has been suggested (Hoyer, 2002). Since insulin, IGF-1, insulin-receptors, and the signalling mechanisms are impaired in AD brain, this entity resembles DM and for that reason Steen et al. (2005) proposed the term "Type 3 Diabetes". However, DAG induces negative energy balance (Asakawa et al., 2005), reduces fat mass (Zhang et al., 2008) and improves insulin sensitivity and glucose homeostasis (Delhanty et al., 2010), besides increasing β-cell mass, function and survival (Granata et al., 2010). Thus, DAG shows a potential to prevent the diabetic-type of neurodegeneration in AD.

Additionally, DM causes diabetic encephalopathy manifested with cognitive impairment (Gispen and Biessels, 2000). Its development is multifactorial, involving both deficiency of brain-derived neurotrophic factor (BDNF) and apoptosis (Ma et al., 2011). BDNF is the most prevalent growth factor in CNS (Barde et al., 1982), strong regulator of neuronal development and synaptic plasticity, well known for its role in the disease pathology (Autry and Monteggia, 2012). BDNF signals through tropomyosin-related kinase B (TrkB) receptor, leading to activation of three different intracellular pathways and augmentation of NMDA-receptor currents (Levine et al., 1998). Each of these signalling pathways confers unique function of BDNF on cells: phospholipase Cγ (PLCγ) pathway activates protein kinase C; phosphatidylinositol 3-kinase (PI3K) activates serine/threonine kinase AKT; and mitogen-activated protein kinase (MAPK) pathway activates several downstream effectors (Mattson, 2008). Interestingly, ghrelin's effects are also based on, at least partly, activation of these pathways (N. Wang et al., 2014; X. Wang et al., 2014) which supports the idea that ghrelin and BDNF are tightly linked together and to neuronal metabolism and plasticity, and play a significant role in maintaining normal memory function.

BDNF promotes neuronal differentiation and survival therefore BDNF-deficiency may contribute to the impaired hippocampal neurogenesis (Rossi et al., 2006) associated with diverse diseases including AD (Nagahara et al., 2009). Indeed, there are lower levels of BDNF in AD brain, suggesting a potential role for compromised neurotrophic support (Phillips et al., 1991). Neurogenesis is activity dependent (Sendtner et al., 2000). As recently shown ghrelin leads to earlier activity onset and higher activity levels (Stoyanova and le Feber, 2014). This local activation induces BDNF production in the postsynaptic neuron (Zafra et al., 1991) which upregulates genes encoding proteins crucial for neuronal survival such as Bcl-2 (Mattson et al., 1995). Neurogenesis involves NO production, which is Ca^{2+} mediated (Lee et al., 2002a). On the other hand, central ghrelin administration increases NO levels in the hypothalamus (Gaskin et al., 2003) therefore, it could be speculated that ghrelin increases intracellular NO levels also in the hippocampus responsible for the effects on memory retention (Carlini et al., 2004).

BDNF mediates the effects of environmental factors on hippocampal neurogenesis, learning and memory. Hippocampal BDNF is increased in response to physical activity (Oliff et al., 1998), dietary restrictions (Lee et al., 2002b) and cognitive stimulation (Young et al., 1999) which enhances synaptic plasticity, neurogenesis, learning and memory and thus reduces the risk of AD (Mattson et al., 2004). BDNF is part of a central mechanism integrating physical activity with elements of energy metabolism to impact cognition therefore proper management of cellular energy is a vital requirement for synaptic function (Gomez-Pinilla et al., 2008). BDNF is also implicated in the long-term potentiation and synaptic plasticity (Figurov et al., 1996), as well as ghrelin (Diano et al., 2006).

Apoptosis contributes to AD neuronal loss (Hroudová et al., 2014). Caspases and Bcl families are important factors regulating apoptosis, and mitochondria are implicated in a variety of key events during it (Chan, 2004). Activation of caspase-3 is the major committed step of apoptosis (Martin, 2001) however, AG inhibits it. AG targets the Bcl-2 family, inhibits the apoptotic cascade and favours cell survival (Zhang et al., 2013). Ghrelin stabilizes mitochondria by reducing ROS production, preserving mitochondrial inner transmembrane potential, and preventing cytochrome-*c* release (Chung et al., 2007).

Oxidative stress and synaptic plasticity are interrelated such that an imbalance in ROS formation influences synaptic plasticity and cognition. Synaptic plasticity and molecules implicated in it such as BDNF are affected by cellular energy metabolism (Wu et al., 2004). Hence, the interaction between oxidative stress and BDNF can be a fundamental mechanism by which ageing affects neuronal plasticity (Cheng and Mattson, 1994). Elevated ROS decrease BDNF expression and synaptic plasticity (Wu et al., 2004) therefore ghrelin with its ability to increase fatty acid oxidation and to buffer ROS can stimulate BDNF production and preserve synapses. These findings also suggest that impairments in ghrelin signalling may contribute to AD pathophysiology (Giordano et al., 2007) and conversely, ghrelin has a potential for treating neuronal damage and cognitive dysfunction (Atcha et al., 2009).

Ghrelin is affected by ageing (Rigamonti et al., 2002) and inhibition of ghrelin signalling results in decreased number of spine synapses in the striatum, followed by impaired performance in memory testing, both of which have rapidly recovered by ghrelin administration (Levi et al., 1990). On the other hand, AD impacts on the ghrelin system at all levels (Gahete et al., 2010). The temporal cortex, which is one of the most important structures for memory and cognition, is also one

of the most affected in AD (Braak and Braak, 1991). In healthy humans, ghrelin, GOAT and GHSR1a are highly expressed in the temporal lobe (Castañeda et al., 2010). However, in AD there is a striking reduction of all of them whereas the expression of GHSR1b is increased, suggesting that these changes in ghrelin system could be involved in the progression of the disease (Gahete et al., 2014). Although plasma ghrelin decreases with age (Rigamonti et al., 2002) AD patients might have a further reduction in local ghrelin production. Since ghrelin levels in the cerebrospinal fluid of AD patients are unchanged (Proto et al., 2006) it is possible that perturbed local ghrelin secretion may be more relevant to the aetiology of the disease (Gahete et al., 2010).

AD is also associated with appetite alterations (Creyghton et al., 2004), named "anorexia of ageing", which is often responsible for the reduced body weight (Morley, 1997). Age-related ghrelin decline might, at least partly, explain the somatotrope dysregulation in older subjects (Rigamonti et al., 2002). Ghrelin responds to changes in energy balance, and its orexigenic effects are mediated by hypothalamic NPY, therefore, the positive correlation between NPY and ghrelin in AD and healthy individuals may reflect the relationship among peripheral and central signals in the control of eating (Proto et al., 2006).

Parkinson's disease

PD has a prevalence of 2% among people over the age of 65 years (Lees et al., 2009), characterised with motor and non-motor dysfunctions. The classical motor symptoms are caused by a neuronal loss in pars compacta of substantia nigra (SN) and depletion of dopamine (DA) in the striatum (Martin, 1999). The motor symptoms manifest relatively late, in stage III of the disease (Braak et al., 2004), after 70–80% loss of striatal DA. The non-motor symptoms precede them and reflect changes in the olfactory bulb and cortex, brainstem sleep regulatory centres and DMNV, as a major source of parasympathetic innervation of GIT. This suggests that the nigrostriatal DA pathway is not involved in the pathogenesis of non-motor symptoms (Bayliss and Andrews, 2013).

Aetiology of PD is believed to involve an interaction between genetic and environmental factors (Horowitz and Greenamyre, 2010). In 10% PD is genetically determined whilst in the majority, it is sporadic and of unknown aetiology (Goldman and Tanner, 1998). Mitochondrial dysfunction, oxidative stress, and aggregates of synaptic proteins α-synuclein and ubiquitin (Spillantini et al., 1997) called Lewy bodies have been implicated in PD pathology (Martinez and Greenamyre, 2012). Exposure to environmental factors, such as pesticides, may increase the risk to develop PD (Gorell et al., 1998) by causing mitochondrial dysfunction, particularly reductions in the activity of complex I (Schapira et al., 1989) which enhances ROS formation (Kushnareva et al., 2002). ATP depletion by itself does not account for neurodegeneration, instead the damage results from oxidative stress (Sherer et al., 2003b, 2007).

Oxidative damage from toxin exposure may explain, in part, α-synuclein aggregation (Betarbet et al., 2000). In PD brain, α-synuclein becomes oxidatively modified and insoluble (Giasson et al., 2000). On the other hand, higher α-synuclein expression can itself cause oxidative damage (Hsu et al., 2000) therefore antioxidants are currently discussed as potential therapies for PD (Sherer et al., 2003a). It is noteworthy to mention that ghrelin activates UCP2-dependent alterations in mitochondrial respiration (Andrews et al., 2005) and thus protects DA function. Additionally, ghrelin is reduced during the pre-motor stage of PD which might increase DA neuron vulnerability and thus contribute to disease progression (Andrews et al., 2009). Indeed, ghrelin-KO or GHSR1-KO mice are more susceptible to DA neuron loss, suggesting that abnormal ghrelin signalling may represent a predisposition for nigrostriatal DA dysfunction (Cai et al., 2012). Furthermore, ghrelin administration prevents MPTP-induced DA death, metalloproteinase-3 expression, microglial activation, and the subsequent release of TNF-alpha, IL-1beta, and nitrite. These data suggest that ghrelin may act as a survival factor for DA neurons by deactivating microglia and preserving mitochondrial respiration which makes it a valuable therapeutic agent for PD (Moon et al., 2009).

Another factor probably implicated in pathogenesis of PD is BDNF because its levels are lower in SN (Murer et al., 2001) and conditional deletion of BDNF reduces the number of DA neurons (Baquet et al., 2005). Conversely, administration of BDNF attenuates the loss of DA neurons (Hyman et al., 1991) which indicates that BDNF is required for their normal development. Additionally, transplantation of modified fibroblasts expressing BDNF into either the striatum or the midbrain attenuates induced DA neuron loss (Levivier et al., 1995), promotes functional recovery from the lesions, and corrects behavioural deficit (Mattson, 2008). Noteworthy, caloric restriction elevates BDNF in striatal neurons, diminishes DA depletion and improves functional outcome (Maswood et al., 2004). Since the low-calorie diet stimulates ghrelin secretion (Rigamonti et al., 2002) and, on the other hand, ghrelin stimulates BDNF production, the underlying mechanism for the neuroprotective effect of BDNF in PD could be based on the interaction between these two regulatory molecules.

The non-motor symptoms have a prevalence of 90% in PD (Weintraub et al., 2008). They comprise loss of appetite and weight, gastrointestinal dysfunction, cognitive impairment, reduced sleep quality and depression.

Weight loss in PD is accompanied by low plasma levels of leptin (Fiszer et al., 2010). Whilst low leptin may reflect the decrease in body fat (Evidente et al., 2001), the low ghrelin is less intuitive and warrants further investigation. Nevertheless, it indicates that ghrelin secretion is disrupted in PD. So far, ghrelin agonists have been successful for treatment of cachexia in cancer patients (Neary et al., 2004), which suggests that ghrelin or agonists could be beneficial to the PD patients as well.

A PD patient has dysglycaemia, abnormal glucose tolerance (Lipman et al., 1974) and insulin signalling, though there is a debate regarding a direct association between PD and type 2 DM (Sandyk, 1993). In DM model there are low levels of insulin, associated with decreased amounts of DA transporter-mRNA and tyrosine hydroxylase-mRNA in SN (Figlewicz et al., 1996). Normally, insulin receptors are abundant in SN, however PD patients display much lower number of them (Figlewicz et al., 2003) and significant insulin resistance (Morris et al., 2008). In addition, postprandial ghrelin response is reduced in PD, and it might qualify as a peripheral biomarker and be of diagnostic or therapeutic value (Unger et al., 2011). Reduced ghrelin might increase the vulnerability of DAc neurons and thus to contribute to the disease progression (Andrews et al., 2009).

PD patients frequently exhibit impaired gastrointestinal motility in all stages of the disease (Natale et al., 2008) resulting in delayed gastric emptying (Marrinan et al., 2014). Its aetiology is multifactorial and related to Lewy bodies' deposition in the enteric nervous system and in brain nuclei. The interactions in this brain–gut axis involve complex synergy between neural and hormonal elements, including ghrelin, and may be the key to understanding the pathogenesis of PD. As mentioned previously, GIT functions are regulated by ghrelin via the vagal nerve. Surprisingly, the myenteric plexus of the stomach (Beach et al., 2010) and the DMNV are two of the first sites where Lewy bodies occur (Unger et al., 2011). It is still unclear if the impaired postprandial ghrelin response is related to a process in the stomach or reflects a perturbed vagal gastric innervation due to PD-related neurodegeneration in the DMNV. Hence, the impaired ghrelin excretion might be used as a peripheral biomarker for early PD (Unger et al., 2011) and ghrelin could be a novel therapeutic strategy to combat neurodegeneration, loss of appetite and body weight associated with PD (Andrews et al., 2009).

Nearly all PD patients suffer from selective cognitive impairments (Zgaljardic et al., 2004). Sufficient severity of it to fulfil criteria for dementia occurs in up to 80% of PD patients (Aarsland et al., 2003). Established phenotype of PD dementia (PDD) or Lewy Body dementia

(LBD) often presents with apathy, delusions, excessive daytime sleepiness, or sleep disorders (Candela et al., 2013). A relatively unique feature of PD is that mood disturbance is associated with a quantitative worsening of cognitive deficits, which suggests that a common mechanism might underlie both (Tröster et al., 1995). Moreover, depression may be a forerunner of dementia (Lieberman, 2006). The causative mechanisms remain complex, since the symptoms reflect brainstem and cortical pathology involving several neurotransmitters, including DA, serotonin, norepinephrine, and acetylcholine (Modugno et al., 2013). Basal forebrain cholinergic system degenerates early in PD and worsens with the appearance of dementia. Their dysfunction may result from DA degeneration (Leverenz et al., 2009).

Ghrelin has neuroprotective and disease-modifying effect in PD (Bayliss and Andrews, 2013). It promotes and protects normal DA function (Schapira et al., 2014), enhances both learning and memory via improved synaptic plasticity, and has a neurogenic capacity (Moon et al., 2014). Therefore, it may be a promising therapeutic agent for treatment of cognitive decline in PD.

The majority of patients with PD suffer from sleep disturbances including insomnia and daytime sleepiness (Ondo, 2014). Several studies have identified a group of DA neurons in the ventral periaqueductal grey matter (vPAG) (Freeman et al., 2001; Saper and Petito, 1982) which appears to be critical for maintenance of sleep–wake behaviour. Approximately 50% of them express *c*-Fos during wakefulness, but none of them during sleep. They have connections with forebrain and brainstem areas involved in control of arousal, with prefrontal cortex (Yoshida et al., 1989), midline and intralaminar thalamus (Takada et al., 1990), and the amygdala (Hasue and Shammah-Lagnado, 2002). Dopamine transporter (Freeman et al., 2001) and receptors (Lewis and O'Donnell, 2000) are present in both the thalamus and the cerebral cortex, suggesting that DA can directly influence thalamo-cortical activity. Ventrolateral preoptic nucleus (VLPO) heavily innervates the lateral PAG and the vPAG/dorsal raphe nucleus, but because VLPO neurons are sleep-active and contain GABA, they inhibit the wake-active DA neurons, promoting sleep (Sherin et al., 1998). This mutually inhibitory circuitry is a component of the flip-flop switch for sleep/wake control (Saper et al., 2005). Depletion of those DRN/vPAG DA neurons may contribute to the excessive daytime sleepiness in PD (Lu et al., 2006).

REM-sleep behaviour disorder (RBD) develops in approximately 35–50% of patients with older-onset PD in the pre-motor stages of the disease. RBD is characterised by dysfunction of systems that produce the normal REM atonia of sleep (Schenck and Mahowald, 2002) and is caused by synucleinopathies (Romenets et al., 2012). Patients with RBD show increased cognitive impairment (Vendette et al., 2007) and a risk of dementia (Postuma et al., 2012). In this regard, the long latency from RBD expression to development of define disease provides a great opportunity to intervene early when protective treatment might be most effective. RBD and early stage PD patients exhibit reduced circulating ghrelin and postprandial ghrelin response. Since ghrelin possesses protective effect on DAergic neurons, the reduced postprandial ghrelin could be a cause for the reduced ghrelin-mediated neuroprotection, and a long-standing increased vulnerability of DA neurons (Unger et al., 2011). On the other hand, in RBD DMNV is affected, whilst SN is not (Kim et al., 2010), suggesting postprandial ghrelin as another candidate for biomarker in early PD.

Huntington's disease

HD is one of the most common inherited NDD manifested by continuous involuntary movements, cognitive and psychiatric symptoms, and autonomic dysfunctions (Landles and Bates, 2004). HD patients also exhibit progressive weight loss, poor glycaemic control (Aziz et al., 2007) and disturbed sleep (Taylor and Bramble, 1997). HD is caused by mutation in gene encoding huntingtin (htt) protein (Andrew et al., 1993). Processing of the mutation is impaired causing intracellular aggregation in striatal, brainstem and cortical neurons (Bates, 2003), combined with a loss of wild-type htt function (Cattaneo et al., 2001). However, neither the normal function of htt nor the basis for such selective vulnerability is fully understood, although several mechanisms such as impaired energy metabolism (Gu et al., 1996), excitotoxicity (Beal et al., 1986), oxidative stress (Nakao and Brundin, 1997), mitochondrial dysfunction (Brouillet et al., 1995) and apoptosis (Portera-Cailliau et al., 1995) have been considered. All these processes may be interrelated because they involve perturb calcium homeostasis (Petersén et al., 2000) which leads to activation of a cascade of reactions such as induction of non-specific permeabilization of the inner mitochondrial membrane (Gunter and Pfeiffer, 1990), uncoupling respiration from ATP synthesis, release of cytochrome-*c*, apoptosis inducing factor and pro-caspase (Green and Reed, 1998). Calcium overload also activates different enzymes involved in cell death and increases ROS production (Reynolds and Hastings, 1995).

HD is particularly interesting NDD because of involvement of neurotrophic factors, mainly the BDNF signalling (Lynch et al., 2007). Normally, htt up-regulates transcription of BDNF however, this activity is lost when it becomes mutated, resulting in BDNF deficiency in the affected brain regions (Ferrer et al., 2000) and death of striatal neurons. Conversely, restoring the normal htt activity increases BDNF production which protects striatal neurons (Canals et al., 2004) and enhances synaptic plasticity (Lynch et al., 2007). Furthermore, manipulations increasing BDNF in the striatum and cortex, including environmental enrichment (Spires et al., 2004), calorie restriction and antidepressant treatment (Duan et al., 2004) forestall the neurodegenerative process. Since ghrelin is one of the factors that serve as molecular interface between metabolism, neuronal and cognitive functions, it could be implicated into the neuroprotective effect of BDNF in HD.

HD is accompanied by considerable weight loss, particularly in the final stage (Kremer and Roos, 1992) however, it is not associated with reduced food intake. On the contrary, HD patients demonstrate rather increased appetite (Trejo et al., 2004). The higher energy expenditure due to involuntary movements does not explain the lower body weight in asymptomatic gene-carriers (Farrer and Yu, 1985) or in the early stage of the disease, when the hipper activity is absent or minimal (Djoussé et al., 2002). The striatum of HD patients expresses decreased levels of full-length htt (Schilling et al., 1995) which precedes the weight loss (Ona et al., 1999) and influences body weight in a dose-dependent manner (A. Aziz et al., 2008; N.A. Aziz et al., 2008). Reduction of mutant huntingtin (mhtt) in the cortex partially improves motor and mental deficits but does not improve neurodegeneration, whereas reduction of mhtt in both cortical and striatal populations ameliorates all behavioural deficits and the selective brain atrophy. It reveals interacting roles of cortical and striatal mhtt in HD pathogenesis, and suggests that the optimal therapeutics have to target mhtt in both neuronal populations (N. Wang et al., 2014; X. Wang et al., 2014).

The extreme weight loss in HD has also been linked to selective neuronal loss in the hypothalamic lateral tuberal nucleus (Djoussé et al., 2002) and to alterations in the hypothalamic functions, leptin and ghrelin levels (Petersén and Björkqvist, 2006). In HD, there is a significant reduction of OXA neurons in LH and disturbance in plasma ghrelin and leptin (A. Aziz et al., 2008; N.A. Aziz et al., 2008). As ghrelin interacts with OXA neurons (Solomon et al., 2007) and OXA suppresses GH secretion (Seoane et al., 2004), the progressive loss of OXA neurons can also account for the association between dysregulated GH and ghrelin secretion in disease severity (Aziz et al., 2010b). Changes in ghrelin dynamics in early stage of HD become more prominent with the progress of disease, which makes ghrelin a potential biomarker to assess it. Moreover, decreased ghrelin could be correlated with the apoptotic processes triggered by mhtt. Noteworthy that one of the earliest events in the pre-symptomatic and early symptomatic stages is transcriptional up-regulation of the caspase 1 gene (Ona et al., 1999). As the disease progresses, the caspase-3 gene get also up-regulated (Chen et al., 2000). As described earlier in this review, ghrelin has the capacity to prevent activation of these pathways (Andrews, 2011; Zhang et al., 2013) and

disrupts apoptosis. Taken together these results suggest that treatment with ghrelin could be beneficial during the early stages of HD when the activation of caspase pathway could be prevented and thus the progression of HD could be restricted.

HD is also characterised by night-time sleep impairment and circadian rhythm disturbances with phase-shift in sleep/wake cycle towards later hours (Aziz et al., 2010a) which may be related to pathology within SCN molecular oscillation (Pallier et al., 2007). However, circadian rhythm alterations rather than sleep impairment per se are related to the cognitive deficit in HD (Aziz et al., 2010a). Since ghrelin is able to affect sleep–wake status and to modulate the circadian system activity it could also be relevant for treatment of HD. However, the sexual dimorphism in the reaction on ghrelin has to be taken into consideration because after low doses of ghrelin sleep is promoted in male subjects but remains unchanged in female individuals (Steiger et al., 2011).

Conclusions

Based on the currently available data, ghrelin seems to be much more than a promoter of feeding and appetite. Ghrelin is involved not only in lipid and glucose metabolism, but also in higher brain functions such as sleep–wake state, learning and memory; it influences mitochondrial respiration and shows neuroprotective effect, takes part in the etiopathogenesis of variety of neuroendocrine and NDD. All these show that ghrelin is an important link between metabolism and neurodegeneration and make it an attractive tool for development of biomarkers or therapeutics for management of disorders, in which cell protection and recruitment of new neurons or synapses are needed.

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