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Role of ghrelin system in neuroprotection and cognitive functions: implications in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a multifactorial progressive neurodegenerative disorder characterized by loss of memory and cognitive deficits, strongly influenced by the metabolic status, in which the impairment of neuropeptides/neurotransmitters systems has been previously observed. Ghrelin is a multifunctional hormone produced in a wide variety of tissues, which has been associated with the progression of obesity and metabolic syndrome, but has been also linked to neuromodulation, neuroprotection and memory and learning processes. In addition, ghrelin system also acts in an autocrine/paracrine fashion where the majority of its components [ghrelin variants (native ghrelin, In2-ghrelin), acylation enzymes (GOAT) and receptors (GHS-Rs)] are expressed in the different regions of central nervous system. In spite of all these pieces of information strongly suggesting a close association between ghrelin system and AD, which could be of pathophysiological relevance, few studies have been addressed to clarify this relationship. In this work, the role of ghrelin system in neuroprotection, memory consolidation and learning is reviewed, and its influence in AD, as well as the regulation of its expression in AD patients, is discussed.

Keywords

Ghrelin; Alzheimer Disease; neuroprotection; memory; learning

1.- Introduction

Ghrelin is a multifunctional 28-amino acid (aa) hormone produced in a wide variety of tissues, including the brain, where it can act as a paracrine/autocrine factor [25]. The native, intact ghrelin molecule is also called unacyl-ghrelin (UAG) because it is commonly

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modified by the ghrelin O-acyltransferase (GOAT) enzyme [20, 41] to generate acyl-ghrelin (AG), which is the natural ligand of the ghrelin receptor [growth hormone (GH) secretagogue receptor type-1a or GHS-R1a] [23]. Ghrelin was originally identified based on its ability to stimulate GH release. However, soon thereafter, the ghrelin system was shown to be involved in a number of divergent functions such as regulation of food intake, body weight gain, insulin release and β-cell survival, adiposity, and the control of energy homeostasis [10, 40]. Consequently, it has been suggested that the dysregulation of ghrelin system could be directly involved in the development of obesity and the metabolic syndrome. Likewise, the ghrelin system has also been shown to be involved in inflammation [2, 24] and neuromodulation [1, 9, 14], and for all these reasons, it has been proposed to play a relevant role in Alzheimer's disease (AD), a dementia syndrome markedly influenced by the metabolic status and inflammation, in which the impairment of several neuropeptides/neurotransmitter systems [15, 18, 37] has been already observed.

With a rapidly growing relevance, AD currently affects nearly 2% of the population in industrialized countries and the risk of AD dramatically increases in individuals beyond the age of 70; indeed, it is diagnosed to more than 50% of people above the age of 85 [18, 30]. Noticeably, AD represents the predominant cause of senile dementia and it is predicted that the incidence of AD will triple within the next 50 years (www.alz.org). Neuropathologically, AD is characterized by the augmented extracellular accumulation of amyloid-β (Aβ) in senile plaques (SP) and the intracellular aggregation of hyperphosphorylated tau protein comprising neurofibrillar tangles (NFTs) [37]. Of note, fibrilar Aβ has been demonstrated to bind to the type B scavenger receptor CD36, leading to microglial recruitment, activation and secretion of pro-inflammatory molecules, which, in turn, induce neural malfunction and death [4]. In all, AD is considered a multifactorial progressive neurodegenerative disorder, clinically characterized by loss of memory and progressive deficits in other cognitive domains and intellectual functions.

In line with the above, recent studies demonstrating that the ghrelin system is also involved in neuroprotection [24-27], as well as in memory and learning processes [30-35], together with the wide distribution of ghrelin system in different areas of the brain [16-23], reinforce the idea of the involvement of changes in this system in the generation and/or progression of the Alzheimer's disease.

2.- Ghrelin system in the brain

Initial studies showed that the overall ghrelin content in the brain is very low [23]. However, application of more detailed specific approaches showed that ghrelin is present in the hypothalamic arcuate nucleus (ARC), where it is especially abundant in the ventral part, an important region in the control of appetite [29]. In addition, a more recent study has reported the presence of ghrelin in previously uncharacterized hypothalamic neurons adjacent to the third ventricle between the dorsal, ventral, paraventricular, and arcuate hypothalamic nuclei [13]. Of note, ghrelin neurons are located not only in hypothalamus, but also in the cortex (sensorimotor area, cingular gyrus), and the fibers of ghrelin neurons in hypothalamus project directly to the dorsal vagal complex (DVC) [21].

On the other hand, the expression of the recently identified GOAT has not been studied in detail in the brain. Although GOAT expression has been reported in the human brain [17], its distribution in different areas or its putative colocalization with ghrelin has not yet been investigated. However, recent studies suggest that in the mouse, rat and human, the widespread distribution of ghrelin expression is mimicked by a widespread expression of GOAT, including stomach, intestine, adrenal, breast, fat, kidney, pituitary or pancreas [16,

20, 27, 41], and, therefore, it is plausible that overlapping patterns of ghrelin and GOAT will be identified in the CNS.

Ghrelin receptors are prominently expressed in different regions of the brain. Indeed, GHS-R mRNA has been reported in the ARC and ventromedial nuclei (VMN) and in CA2 and CA3 regions of the hippocampus, in the substantia nigra, the ventral tegmental area, the dentate gyrus of the hippocampal formation, and the dorsal and median raphe nuclei [19, 34]. Consistent with these data, GHSR immunoreactivity was detected in neurons throughout the rostrocaudal extent of the VTA and substantia nigra of mice and rats [1]. Unfortunately, the precise types of neurons that express GHS-Rs have not yet been identified.

3.- Ghrelin and neuroprotection

In the last 5 years, the neuroprotective capacity of ghrelin has been assessed using the ischemia paradigm. *Ischemia* is a condition in which blood flow (and thus oxygen and glucose) is restricted in the brain. The precise mechanism of ischemia-induced neuronal death is not clear; however, apoptosis is one of the mechanisms involved [31].

Since the hypothalamus is one of the main brain targets for ghrelin actions in the regulation of food intake and metabolic regulation, the first studies to investigate the neuroprotective role of ghrelin where carried out in this brain area. In 2006, Liu et al. analyzed for first time the effect of ghrelin in tolerance of the brain tissues to cerebral ischemia/reperfusion (I/R) injury [28]. Specifically, when ghrelin was administered after the injury in rats, it was able to significantly increase the number of surviving neurons and reduce the number of apoptotic neurons in CA1 area of the hippocampus [28].

Subsequently, in vitro studies on primary hypothalamic neurons exposed to oxygen-glucose deprivation (OGD) further support a neuroprotective role of ghrelin. Specifically, treatment of hypothalamic neurons with ghrelin inhibited OGD-induced cell death and apoptosis through a rapid activation of ERK1/2. Ghrelin exerted these actions by inhibiting generation of reactive oxygen species and stabilizing mitochondrial transmembrane potential. In addition, ghrelin-treated neurons showed an increased Bcl-2/Bax ratio, a reduced cytochrome c release, and reduced caspase-3 activation [11].

Of note, the neuroprotective actions of ghrelin on hypothalamic neurons were soon thereafter extended to cortical neurons. Specifically, Miao *et al*. showed that ghrelin, injected intravenously, has neuroprotective effects in transient focal I/R injury in rats [32]. Moreover, similar to hypothalamic neurons, ghrelin exerts its neuroprotection in cortical neurons by inhibiting pro-apoptotic molecules associated with mitochondrial pathways and by activating endogenous protective molecules [32].

Interestingly, it has been reported that ghrelin acts as a survival factor for cortical neuronal cells by inhibiting apoptotic pathways regardless of its acylation [12]. Thus, AG and DAG protect cortical neurons from the injury induced by in vivo transient focal cerebral I/R by suppressing the expression of Par-4, a proapoptotic gene. In both cases, the neuroprotective effects were associated with the upregulation of Bcl-2/Bax ratio, and inhibition of cytochrome c release and caspase-3 activation [22]. However, the neuroprotective effect of AG is mediated via the activation of GHSR-1a, while that of DAG is not [12]. Interestingly, UAG has been recently shown to act as a “neuroprotective” molecule likely through binding to the previously mentioned CD36 scavenger receptor, which interferes in the initiation of signaling cascades that lead to neuronal dysfunction and death [4].

4.- Ghrelin and memory and learning

Ghrelin has been shown to regulate brain functions since, for example, intracerebroventricular (icv) application of AG in rats has an anxiogenic effect (it increased freezing in the open field and decreased the number of entries into the open spaces) [8]. Specifically, ghrelin modulates cognitive processes, not only in the hypothalamus but also in other brain areas. Initial studies demonstrated that icv application of AG increased in a dose-dependent manner the latency time in the step-down test in rats, demonstrating a stimulatory effect on memory retention [7]. Subsequently, the same group demonstrated that the effect of AG on memory retention was independent of the brain area where it is injected (hippocampus, amygdale, or dorsal raphe) [8]. Further studies demonstrated that AG induces memory retention through processes that could include the promotion of synaptic plasticity. One of the initial pieces of evidence supporting the role of ghrelin in neuronal plasticity was reported by Abizaid et al. in midbrain neurons [1]. In this study, they showed that in mice and rats, ghrelin bound to neurons of the ventral tegmental area (VTA) and, in a GHSR-dependent manner, increased dopamine neuronal activity, synapse formation and dopamine turnover in the nucleus accumbens [1].

Similar results have been observed with hippocampal neurons, where systemic injection of AG promoted dentritic spine synapse formation and generation of long-term potentiation [14]. In addition, a single infusion of AG, but not DAG, into the dentate gyrus of the hippocampus caused a long-lasting potentiation of the amplitude of the population spike and of the slope of the excitatory postsynaptic potentials, probably through PI3K signaling. This suggests that AG can enhance synaptic plasticity by mechanisms involving both presynaptic (enhancing presynaptic excitatory inputs) and postsynaptic (elevating excitability of postsynaptic neurons) mechanisms [9]. Interestingly, these ghrelin-induced synaptic changes were closely paralleled by enhanced hippocampus-dependent spatial learning and memory. In support of these data, ghrelin knock-out (KO) mice have been reported to exhibit decreased numbers of spine synapses in the CA1 region and impaired performance in behavioral memory testing, two deficits which were reversed by ghrelin administration [14].

More recently, studies by different groups have demonstrated that icv infusion of AG reversed the impairment in object recognition memory in food-restricted female mice [6] and intraamygdaloid AG injection in male rats enhances learning processes and memory in aversive situations, as shown by the step-through passive avoidance and the Morris water maze paradigms [38, 39]. Finally, intra-hippocampal AG administration prior to a training session improved the long term memory in this task, but did not modify the short term memory [5]. Taken together, these results suggest that AG may modulate specific molecular intermediates involved in memory acquisition/consolidation but not in the retrieval, through processes that could include the promotion of synaptic plasticity.

5.- Ghrelin system in Alzheimer’s disease (AD)

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 abnormalities in learning and memory related to abnormalities in septo-hippocampal function, which are due to overproduction of β-amyloid. In this mouse model, ghrelin was able to improve retention of T-maze foot shock avoidance in 12 and 14 month-old mice, compared to their controls [14]. More recently, a different mouse model has been used to analyze in more detail the role that ghrelin plays in AD-related endpoints. This model was generated by intrahippocampal injection of oligomeric forms of the Aβ peptide (AβO), which have been directly related with AD-associated damage [33]. Results of this study revealed that

systemic injection of ghrelin rescues memory deficits observed following intrahippocampal AβO injection, using two independent behavioral paradigms (Y-maze and passive avoidance tasks). In addition, the AD-associated neuropathological abnormalities observed in these AβO mice were also attenuated by ghrelin. Indeed, ghrelin inhibited the reactive microgliosis originated by AβO, thus preventing the inflammatory response. Ghrelin also prevented AβO-induced neuronal cell loss in the dentate gyrus and increased the density of hippocampal synaptic and cholinergic nerve fibers. Collectively, these data show that systemic injection of ghrelin rescue cognitive impairments induced by AβO, possibly through inhibition of both, microgliosis and impairment of neuronal integrity [33].

In spite of the growing body of evidence pointing out the strong relationship between ghrelin system and metabolism, inflammation, neuroprotection, and memory and learning processes, only few studies have been conducted to date to unveil the potential implication of the ghrelin system in human Alzheimer's disease. In 2002, it was reported that mean plasma ghrelin concentrations in older normal weight subjects were significantly lower than those present in young normal weight subjects, providing the first evidence for an age-related decline of plasma ghrelin concentrations [36]. Nevertheless, a more recent study has reported that ghrelin levels do not vary in the cerebrospinal fluid of AD patients compared with age-matched controls [35].

However, until 2010, the effects of AD on the expression of the ghrelin system in the brain had not been explored. In a recent study, our group 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 the temporal lobe is considered as one of the most important cortical structures in memory and cognition, and is one of the most affected regions in AD [3]. This report showed, for the first time, that AD patients have a reduction in local brain ghrelin production, as compared with age-matched controls [17]. In addition, we analyzed the expression of a newly described In2-ghrelin splice variant, which could also be acylated by the ghrelin-O-acyltransferase (GOAT) enzyme. Results revealed that, similar to ghrelin, In2-ghrelin variant is also expressed in the temporal lobe, and is down-regulated in AD, thereby showing, together with ghrelin, a region-dependent alteration with AD [17]. Consistent with a similar distribution between ghrelin and GOAT in other tissues, GOAT was also expressed in the temporal lobe of the brain and was impaired in AD [17], suggesting that a functional autocrine and/or paracrine pathway might be in place within the temporal lobe, and that changes in locally-produced acylated/non-acylated ghrelin and In2-ghrelin variant may be of (patho)-physiologically relevance.

In keeping with the results observed for the peptides and their acylation partner, our study also revealed that GHS-R1a, which is expressed at high levels in all regions of the temporal lobe, is altered in AD patients, showing a region-dependent reduction in its expression levels [17]. Of note, human GHS-R1a is encoded by a gene that also produces an alternative spliced variant (GHS-R1b), which may serve as a dominant negative inhibitor of GHS-R1a [26]. Interestingly, GHS-R1b was found to be clearly expressed in the three different regions of the temporal lobe, at levels comparable to that of GHS-R1a; however, its expression level was clearly increased in all the regions of AD patients [17]. These results suggest that AD induces a striking reciprocal shift in the mRNA pattern of GHS-R1a and GHS-R1b, where GHS-R1b is the dominant isoform in AD samples. Since GHS-R1b can heterodimerize with GHS-R1a, promoting translocation of the receptor complexes and thereby acting as a dominant-negative receptor, it can be speculated that this increase in GHS-R1b mRNA levels may effectively contribute to counteract the normal ghrelin/GHS-R1a signaling.

Consequently, the reduction in the ghrelin and GOAT expression levels, together with the shift in the GHS-R1a/GHS-R1b expression ratio suggests dramatic disruption of the ghrelin

autocrine/paracrine loop in the temporal lobe of AD patients, which may contribute to the impairment in the memory and learning processes observed in these subjects. However, future work will be necessary to unequivocally establish the precise role of the ghrelin system in AD.

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Highlights

AD is a progressive neurodegenerative disorder influenced by the metabolic status.

Ghrelin system is linked to obesity, metabolic syndrome, neuromodulation and memory.

Ghrelin system acts autocrinely/paracrinely and its components are expressed CNS.

We review the role of ghrelin system in neuroprotection, memory and learning.

We discuss the influence of ghrelin system in AD, and its expression in AD patients.