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Review article

The neurological effects of ghrelin in brain diseases: Beyond metabolic functions

Qian Jiao[a,b,1], Xixun Du[a,b,1], Yong Li[a,b], Bing Gong[a], Limin Shi[a,b], Tingting Tang[a,b], Hong Jiang[a,b,*]

[a] Department of Physiology, Shandong Provincial Key Laboratory of Pathogenesis and Prevention of Neurological Disorders and State Key Disciplines: Physiology, Medical College of Qingdao University, Qingdao, China
[b] Shandong Provincial Collaborative Innovation Center for Neurodegenerative Disorders, Qingdao University, Qingdao, China

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ABSTRACT

Ghrelin, a peptide released by the stomach that plays a major role in regulating energy metabolism, has recently been shown to have effects on neurobiological behaviors. Ghrelin enhances neuronal survival by reducing apoptosis, alleviating inflammation and oxidative stress, and accordingly improving mitochondrial function. Ghrelin also stimulates the proliferation, differentiation and migration of neural stem/progenitor cells (NS/PCs). Additionally, the ghrelin is benefit for the recovery of memory, mood and cognitive dysfunction after stroke or traumatic brain injury. Because of its neuroprotective and neurogenic roles, ghrelin may be used as a therapeutic agent in the brain to combat neurodegenerative disease. In this review, we highlight the pre-clinical evidence and the proposed mechanisms underlying the role of ghrelin in physiological and pathological brain function.

Contents

Abbreviations: ACCα, acetyl-CoA carboxylase α; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AMPARs, α-amino-3-hydroxy-5- methyl-4-isoxazole propionic-type receptors; AgRP, agouti-related protein; AMPK, adenosine monophosphate-activated protein kinase; ARH, arcuate nucleus of hypothalamus; ATF, activating transcription factor; BBB, blood–brain barrier; CaMKII, Ca^{2+}/calmodulin dependent protein kinase II; CART, cocaine and amphetamine regulated transcriptpeptide; DG, dentate gyrus; DMN, dorsomedial nucleus; DMV, dorsal motor nucleus of vagus; ER, endoplasmic reticulum; ERK1/2, extracellular regulated protein kinases1/2; GH, growth hormone; GHRH, growth-hormone-releasing hormone; GHS-R1a, growth hormone secretagogue receptor type1a; GHS-R KO, GHS-R gene knockout; GIT, gastrointestinal tract; GKO, ghrelin gene knockout; GluA1, AMPA receptor subunit GluR1; GOAT, ghrelin *O*-acyl-transferase; GSK, glycogen synthase kinase; HPA, hypothalamus-pituitary-adrenal; IBI, ischemic brain injury; i.c.v, Intracerebroventricular; IGF, insulin-like growth factor; IL, interleukin; iNOS, inducible nitric oxide synthase; JAK, Janus kinase; KA, kainic acid; Kv7/KCNQ/M KO, Kv7/KCNQ/M gene knockout; LH, lateral hypothalamus; MPTP, 1-methyl-4-phenyl-1 2 3 6-tetrahydropyridine; MCAO, middle cerebral artery occlusion; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; NF-κB, nuclear factor-kappa B; NPY, neuropeptide Y; NSCC, nonspecific action current; NS/PCs, neural stem/progenitor cells; NST, nucleus of the solitary tract; OB, olfactory bulb; OGD, oxygen-glucose deprivation; OS, oxidative stress; Par-4, prostate apoptosis response-4; PD, Parkinson's disease; PI3, phosphatidylinositol 3; PI3 K/Akt, phosphatidylinositol 3-kinase/Akt; PI-PL, phosphatidylinositol-specific phospholipase; PKA, protein kinase A; PKC, protein kinase C; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; RMS, rostral migratory system; ROS, reactive oxygen species; SIRT1, sirtuin1; SNpc, substantia nigra pars compacta; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; SVZ, subventricular zone; TBI, traumatic brain injuries; TNF, tumor necrosis factor; THA, threohydroxyaspartate; UCP2, uncoupling protein 2; VMN, ventromedial nucleus; VTA, ventral tegmental area.

* Corresponding author at: Department of Physiology, Shandong Provincial Key Laboratory of Pathogenesis and Prevention of Neurological Disorders and State Key Disciplines: Physiology, Medical College of Qingdao University, Qingdao, China.
E-mail addresses: jiaoqian2006@126.com (Q. Jiao), xunxundu@163.com (X. Du), liyong_55@sina.cn (Y. Li), gongxian666@163.com (B. Gong), slm0532@163.com (L. Shi), sunnyting1230@126.com (T. Tang), hongjiang@qdu.edu.cn (H. Jiang).
[1] These two authors contribute equally to this paper.

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1. Introduction

Ghrelin, a brain-gut peptide mainly released by X/A-like cells of the stomach, is the unique endogenous ligand for the growth hormone secretagogue receptor type 1a (GHS-R1a) and plays a fundamental role in regulating energy homeostasis (Kojima et al., 1999; Muller et al., 2015). The active acyl-ghrelin modified by ghrelin *O*-acyl-transferase (GOAT) in Ser3 is excreted into the circulation and crosses the blood-brain barrier (BBB). Besides expression in the stomach, ghrelin is also expressed in the brain and other organs (Date et al., 2000; Ferrini et al., 2009; Korbonits et al., 2001; Moretti et al., 2014; Muller et al., 2015). In the brain, ghrelin is found in several neural locations, such as the arcuate nucleus of the hypothalamus (ARH), the ependymal layer of the third ventricle, the dorsomedial nucleus (DMN), the hypothalamus, the paraventricular nucleus (PVN), the ventromedial nucleus (VMN) and the ventral tegmental area (VTA) (Abizaid, 2009; Hou et al., 2006; Mondal et al., 2005). The secretion of ghrelin is complex and influenced by various stimuli, including fasting, blood sugar, somatostatin analogues, insulin, drug addiction, stress, and diseases (as reviewed in (Panagopoulos and Ralevski, 2014)), and others (Cummings et al., 2001; Li et al., 2015; Szulc et al., 2013; Topyildiz et al., 2016). Ghrelin levels in serum increased during fasting and decreased after food intake or oral glucose administration (Tschop et al., 2000). An increase in preprandial ghrelin level has been recorded, which is subsequently followed by a sharp postprandial decline in humans.

2. Ghrelin and brain-gut axis

Brain-gut axis contains three main sites: the gastrointestinal tract (GIT), the central nervous system and the enteric nervous system, and plays important role in the maintenance of glucose and energy homeostasis (Konturek et al., 2004; Migrenne et al., 2006). Brain and gut use the two-way communication that includes vagal and splanchnic nerves (Konturek et al., 2004). Vagal nerve contains both efferent and afferent fibers. Metabolic signals from the GIT are transmitted to the brain by vagal afferents. Activation of the vagal afferents forms a reflex pathway *via* the nucleus of the solitary tract (NTS) and dorsal motor nucleus of the vagus(DMV) (Avau et al., 2013). The parasympathetic (cholinergic) nerves from DMV may regulate ghrelin release. It has been reported that ghrelin level was decreased in a short time, and GSH-R expression in the small intestinal muscle layers was down-regulated after vagal nerve injury in rats (Williams et al., 2003; Yang et al., 2011a). Parallel evidences also showed that the gastric vagal afferent blockage could abolish ghrelin-induced physiological activities, such as growth hormone (GH) secretion and feeding (Date et al., 2002a). On the other hand, one study showed that using an isolated anterior pituitary cell perfusion system, ghrelin-induced GH release was weaker than that *in vivo* (Yamazaki et al., 2002). This suggested that ghrelin stimulates GH release in an indirect route in which pituitary existed

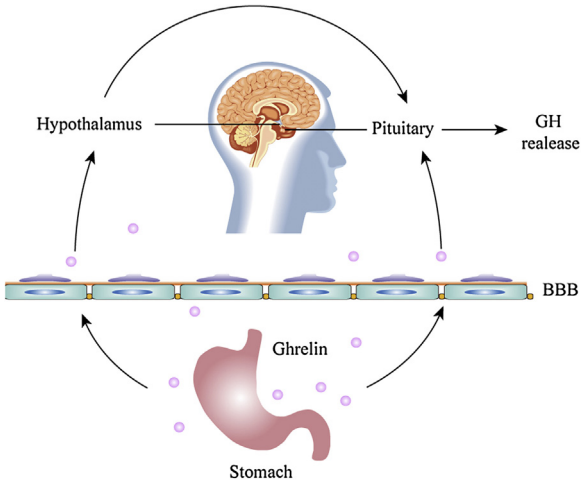

Fig. 1. GH release is regulated by ghrelin.
Ghrelin derived from stomach could cross the BBB. Ghrelin binds with GSH-R1a in the hypothalamus, which results in releasing of GH in the pituitary. Ghrelin can also bind with GSH-R1a in the pituitary to regulate GH release directly.

(Yamazaki et al., 2002). Moreover, the GHS-R mRNA is expressed in nodose ganglion cells, which are the stomach-projected afferent nerve in the rat (Sakata et al., 2003). These together suggest that ghrelin signals from the gastrointestinal were transmitted to the brain mainly through vagal afferent nerves (Sakata et al., 2003).

In total ghrelin, about 99% was from GIT. In human, 60%–75% ghrelin in the circulation were from stomach system and plasma ghrelin levels in totally gastrectomized patients were reduced to 35% of normal (Ariyasu et al., 2001; Seim et al., 2012). In addition, the concentration of ghrelin in the circulation was reduced to 20% of normal following acid-producing part removal of the stomach (Dornonville de la Cour et al., 2001). About 30% ghrelin derived from small intestine (Cummings and Shannon, 2003; Gualillo et al., 2003). Although ghrelin can modulate gastric acid secretion, motility and colonic motility in periphery, another important role of ghrelin in the brain-gut axis is to regulate food intake, body weight, adiposity and blood glucose in CNS (Delporte, 2013; Fujino et al., 2003; Tebbe et al., 2005). Peripheral ghrelin, as well as hypothalamic derived ghrelin, binds with GHS-R1a in the anterior pituitary to stimulate the secretion of GH (Fig. 1), which is distinct from its regulation by hypothalamic growth-hormone-releasing hormone (GHRH) (Chanoine et al., 2009; Kojima et al., 1999; Muller et al., 2015; Schmid et al., 2005). Administration of 1.0 mg/kg ghrelin to adult human could markedly and long-lasting increase much higher plasma GH levels than the equal dose of GHRH-29 (Arvat et al., 2000). In CNS, ghrelin also binds GHS-R1a on vagal afferent neurons, for example, ARH neurons, and stimulates neuropeptide Y (NPY) and agouti-related protein (AgRP) release (Fig. 2) (Nakazato