The Brain-Stomach Connection

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Abstract
The stomach-brain connection has been revealed to be one of the most promising targets in treating obesity. The stomach plays a key role in the homeostatic mechanism implicating stomach-brain communication regulated under neural and hormonal control. The present review explores specific topics related to gut-brain interactions focus on the stomach-brain connection through the different known systems implied in energy balance control as ghrelin, and nesfatin. Moreover, novel mechanisms for energy balance regulation involving gastric-brain communication are described including the role of the gastric intracellular mTOR/S6K1 pathway mediating the interaction among ghrelin, nesfatin and endocannabinoid gastric systems to modulate metabolism.

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Obesity constitutes a major public health problem in the developed countries. However, currently employed therapies are not successful with the exception of gastric surgery, which, at present, is the most effective treatment for this pathology. This finding suggests that the signals from the gastrointestinal tract are crucial for the regulation of energy balance. Recent progress in the fight against obesity has involved investigating the increasing number of peripheral hunger and satiety signals that require central integration. In this context, the stomach-brain communication has been revealed to be one of the most promising targets in treating obesity.

Immediately after ingestion, nutrients interact with different areas of the gastrointestinal tract, which respond by secreting various hunger and satiety signals that require central integration to allow efficient energy homeostasis. These neurohormonal signals communicate nutritional status to the brain centers.
In this scenario, the stomach plays a key role in the homeostatic mechanism, implicating stomach-brain communication, which is regulated under neural and hormonal control and is responsible for maintaining body weight.

**Neural Control of the Brain-Stomach Connection**

The stomach is not only a reservoir of food but is also a complex, highly regulated organ with a neural mechanism that connects with higher brain areas, which are associated with central functions, such as reward and appetite [1]. In this context, the neural control of this regulatory system is managed by the nervous system and affects the gastrointestinal tract (fig. 1). The neural control of the gastrointestinal tract is exerted by the autonomic nervous system innervating the stomach, which can be further divided into the sympathetic (excitatory innervations) and the parasympathetic (inhibitory innervations) divisions of the nervous system [1]. The parasympathetic division is composed of the vagal and pelvic nerves, and the sympathetic division includes the splanchnic nerves.

The vagus nerve has recently been shown to regulate energy homeostasis as a mediator of the interaction between stomach and brain [2]. Food-related stimuli activate

![Fig. 1. Neural control of the brain-stomach connection (see text for details).](image-url)
the sensors of the afferent fibers in the stomach modulating gastrointestinal tract functions and food intake [3]. The afferent fibers of the vagus reach the dorsal brainstem, primarily the nucleus of the solitary tract, and from here to different brain centers as the hypothalamus, to modulate orexigenic and anorexigenic signals in charge of regulate energy (fig. 1) [1].

The enteric nervous system is composed by a complex network of nervous cells located in the gastrointestinal tract. This system is required for major gastrointestinal functions as gut motility, secretion and blood flow [4]. The neurons from the enteric nervous system innervate the stomach and are localized in the myenteric and the submucous plexus. The submucous plexus is primarily involved in responding to nutrient signaling, whereas the myenteric plexus is primarily involved in the coordination of motility patterns [3]. It was recently demonstrated that the myenteric plexus is endowed with a medium-term memory, suggesting that enteric neurons have an intermediate-term memory [5].

**Hormonal Control of the Brain-Stomach Connection**

The gastrointestinal tract has been revealed as the largest endocrine organ in the body. More than 30 different gastric-derived peptides are secreted from enteroendocrine cells in response to ingested food regulating, in addition to digestive functions, energy balance [6]. These functions are, in part, mediated by the action of the gastric-derived peptides at a central level and, especially, in the hypothalamus, the main center regulator of appetite. At the hypothalamic level, the arcuate NPY/AgRP neurons are in charge of sensing and responding to a wide variety of hormones and nutrient-derived signals in the blood that are relevant to both the short- and long-term aspects of energy homeostasis (fig. 1) [7].

In this context, the gastrointestinal-derived peptides involved in the control of energy homeostasis have recently garnered a notable degree of attention. Among these peptides, ghrelin is considered the most relevant, as demonstrated by the considerable volume of works published about this hormone and its actions [8]. In addition, nesfatin-1, a stomach-derived peptide involved in food intake regulation, which was recently discovered, is receiving increasing interest as a regulator of energy homeostasis [9].

**Ghrelin**

Ghrelin was isolated from the stomach in 1999 by Kojima et al. [10] as an endogenous ligand for the growth hormone secretagogues orphan receptor. Thirty percent of the circulating levels of this 28-amino-acid peptide present acylation by an n-octanoic acid in the Ser3 residue. The remaining 70% circulates as unacylated ghrelin. The
acyltransferase that catalyzes ghrelin octanoylation has recently been identified as ghrelin O-acyltransferase and appears to be a key factor in ghrelin function [11].

In humans and rodents, ghrelin-circulating levels were decreased by 65% after gastrectomy, suggesting that the stomach is the main source of ghrelin in the organism. In particular, the main ghrelin-producing cells in the stomach are X/A-like cells, although ghrelin expression throughout the entire gastrointestinal tract has also been described [11]. In addition, ghrelin expression has also been detected in other tissues, such as the hypothalamus, pituitary, ovary, testis, heart and placenta [11].

The diversity of ghrelin physiological actions underlines the key role of the stomach in energy balance regulation. Following exogenous administration of ghrelin, its neuroendocrine functions and effects on GH secretion, as well the corticotroph axis and prolactin secretion were shown [12]. The effects of ghrelin on the digestive tract include an increase of gastric acid secretion and gastric motility. In addition to these functions, this peptide is involved in vasodilatation and cellular proliferation [12].

Ghrelin constitutes the main gastric-derived peptide regulating energy balance as a connection between the stomach and brain. In fact, it has been reported that AgRP/NPY neurons are the primary targets of ghrelin orexigenic actions in the hypothalamus (fig. 1) [7].

Gastric Ghrelin Regulation

Regulation of endogenous ghrelin levels are influenced by chronic or acute nutritional status changes in animals and humans. Thus, in food deprivation conditions ghrelin levels are elevated in plasma, while low levels of this peptide are seen after feeding [5]. Until recently, the mechanism that directly regulates ghrelin production in the stomach remained unclear, leading to the assumption that any changes in plasma ghrelin reflect changes in gastric ghrelin release.

In 2007, a novel organ culture model was developed assessing gastric ghrelin secretion directly from gastric tissue explants [5]. Using this new system, it was demonstrated that food-mediated changes in plasma ghrelin levels are due to variations in ghrelin release by the stomach [5]. In addition, it was further demonstrated that the effect of food intake on circulating ghrelin levels involves a more complex mechanism of action than previously thought. In the mentioned article, it became clear that the ghrelin secretion directly from the stomach is not only due to direct mechanical contact with the gastric wall, digestion or absorption of nutrients. The exposure to food-related sensory stimuli, without real intake, is able to modify gastric ghrelin secretion and its circulating levels, in the same way as true feeding [5]. This fact indicates that a relevant factor involved in this process are the central nervous system sensorial stimuli, including ghrelin as a neural-mediated integrative factor that constitutes a link between the sensory qualities of food, neural activation and nutrient metabolism. Furthermore, the regulation of ghrelin production by sensory stimulus is blocked after surgical vagotomy in rats implying the mediation of vagus nerve in ghrelin action [5].
In addition to the implication of the vagus nerve in the gastric control of ghrelin production, it has been demonstrated that the neuronal network of the myenteric plexus is endowed with medium-term memory. Seoane et al. [5] reported that gastric tissue excised from the organism that maintained the previous secretor status for a period of 3 h after excision, suggesting that the neurons from the enteric system of the gastric tissue have medium-term memory. These data were supported by previous studies demonstrating that synaptic activity memory exists in the enteric nervous system.

In addition to food intake-related factors, other metabolic stimuli, such as the classical components of the somatotrope axis pathways, are implicated in gastric ghrelin regulation. These factors comprise somatostatin (SS), growth hormone-releasing hormone (GHRH), insulin-like growth factor 1 (IGF-1) and growth hormone (GH) [13]. It has been demonstrated that SS and GH in vitro inhibits gastric ghrelin secretion though specific receptors for both hormones in the stomach [13].

Nesfatin-1

Nesfatin-1 is an 82-amino-acid peptide identified in 2006 by Oh-I et al. [14] that is derived from a 396-amino-acid precursor, nucleobinding protein 2 (NUCB2), which, after processing, produces three different subtypes: nesfatin-1, nesfatin-2 and nesfatin-3. Currently, only nesfatin-1 has been demonstrated to have an effect on metabolism regulation.

The expression of NUCB2 was initially found in the hypothalamic nucleus involved in food intake control and co-expressed with other appetite-regulator peptides (MCH, CART, α-MSH and NPY). However, recently, it was demonstrated also to be expressed in other brain areas together with other hypothalamic peptides involved in pituitary hormonal secretion, such as CRF, TRH, GHRH and SS and stress response (neurotensin, CRF, serotonin) [15]. At the peripheral level, nesfatin-1 expression has been described in different organs, such as the stomach, heart, pancreas, testis, pituitary and adipose tissue. Co-expression of nesfatin-1 with ghrelin in the stomach and pancreas has been described [16].

The first physiological function described for nesfatin-1 was the reduction of food intake in the dark phase after central injection in rats. In addition, a reduction in weight gain and fat depots most likely related to the anorexigenic action was also observed [14]. In this context, all of the evidence suggests a physiological role for nesfatin-1 as a negative regulator of food intake [16].

With respect to nesfatin-1 production regulation, higher levels of expression in the brain have been found in the hypothalamic nucleus, which suggests a potential role in food intake and metabolism regulation. Moreover, this peptide’s hypothalamic levels vary with energy status modifications, being inhibited in fasting or under food deprivation and increased after refeeding. However, contradictory effects have been