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Gastrointestinal Hormones and the Gut Connectome

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Abstract

Purpose of review—Provision of adequate nutrients by the gut is essential for survival and essential behaviors are linked to the proper ingestion and digestion of food. Recently, a new neural connection has been reported between sensory cells of the gut epithelium and the nervous system that mediates signals from the gut to the brain.

Recent findings—This review describes how the gut senses its environment, relays those signals to the brain, and how the brain influences the gut.

Summary—This gut-brain connection provides a pathway for how the body handles food.

Keywords

enteroendocrine cell; microbiota; hormone; neuron; neuropod; glia

Introduction

Different from other peripheral tissues, the gastrointestinal (GI) tract is exposed to a unique chemical and microbiota rich environment. In addition, the contents of the GI tract are constantly modified by eating, replication and metabolism of microorganisms, and even pharmaceutical treatments. Besides these internal modifications, GI contents are also shaped by our culture and social environment and exhibit a unique personal signature.

In order to cope with such an active, changing and complex environment, the GI tract has developed sensing mechanisms to accurately detect and respond to enteric contents [1]. Peripheral sensing is relayed to the brain through the nervous system where electrical signals are interpreted by the brain. Sensing in the gut is conveyed by the enteric nervous system (ENS). The ENS is comprised of 200–600 million neurons which is equivalent to the number of neurons in the spinal cord, therefore, it is not surprising that the ENS has been referred to as the “second brain”[2, 3]. However, it is apparent that the ENS alone is insufficient to carry all of the signals from the gut but involves an integration of signals from nerves with enteroendocrine, immune, and epithelial defense systems[1, 4]. This review will focus on the relationship between the enteroendocrine and enteric nervous systems.

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Enteroendocrine cells and gut hormones

Enteroendocrine cells are single cells scattered throughout the gut epithelium. Traditionally, 12 major enteroendocrine cells were classified based on their hormone secretion[5]. However, it is now clear that the single hormone classification system for enteroendocrine cells is inappropriate. For example, CCK-containing cells, classically referred to as I cells, have been found to express serotonin, GIP, PYY and ghrelin[6]. Similarly, L cells which were traditionally considered to produce GLP-1, GLP-2 and PYY have been found to also secrete other hormones like GIP and CCK[7]. In addition to hormones, enteroendocrine cells have been shown to express classic neurotransmitters and neuropeptides[8–10]. Because hormones have different effects it is difficult to understand why multiple hormones are produced in the same cell and how secretion of these hormones is regulated. However, high resolution confocal microscopy now has revealed that different hormones and neurotransmitters within the same enteroendocrine cell are stored separately in different subcellular components [11, 12]. Therefore, it is possible that hormones can be differentially released from a single enteroendocrine cell following a unique stimulus.

Enteroendocrine cells possess unique cell surface receptors that allow them to respond to a variety of stimuli. These receptors allow enteroendocrine cells to sense a broad range of signals including: nutrient, taste, mechanical, and physicochemical stimuli, as well as internal secretion, microorganisms and toxic compounds. The molecular codings underlying enteroendocrine cell sensing are varied and complex. For example: the nutrient sensing mechanisms in enteroendocrine cells include the following categories: free fatty acid receptors (FFAR1-3, GPR119, GPR120, ILDR1[13]), carbohydrate receptors (T1R2-T1R3, SGLT1), peptide and amino acid receptors (CasR, LPAR5, GPR92, GPR93, GPRC6a, T1R1-T1R3), and phytochemical receptors (transient receptor potential (TRP) receptors, T2R, olfactory receptors)[1, 14]. In addition, multiple sensing receptors are expressed in the same enteroendocrine cell. For example: CCK-expressing cells in the proximal intestine have bitter taste receptors, amino acid receptors, free fatty acid receptors, TRPA1, as well as toll-like receptors (TLRs) for microbe sensing[15–18]. Thus, the heterogeneity of sensing receptor expression in enteroendocrine cells, allows them to monitor their specific environment. The complex assembly of receptors and chemical transmitters in enteroendocrine cells make them ideal gut sensory cells, with the ability to detect different luminal contents, encode this information using different transmitters, and then send those signals to the body through secretion of hormones or release of neurotransmitters to the nervous system.

Enteric nervous system and the gut connectome

Two main cell types comprise the enteric nervous system: neurons and glia. Both enteric neurons and enteric glia arise from progenitors that migrate into the gastrointestinal tract from the neural crest during early development. The migration and differentiation of neural crest stem cells are orchestrated by a number of intrinsic and extrinsic molecular factors[19]. The enteric nervous system develops throughout childhood and is stabilized during adolescence[20–23]. Distinct from other peripheral tissue, the enteric nervous system is composed of both extrinsic and intrinsic neural pathways[2]. The extrinsic neural pathway

includes both afferent and efferent vagal and spinal innervation with the nerve bodies outside of the intestinal gut wall. The intrinsic neural pathway in the GI tract is composed of afferent neurons, interneurons, and efferent neurons. The intrinsic pathway allows the GI tract to partially maintain its function in the complete absence of CNS input. On the other hand, the extrinsic pathway allows the CNS to directly and indirectly survey the GI tract and provide constant modification of intrinsic nervous activity. In order to adequately sense and respond to the complex contents within the gut lumen, the intestinal mucosa is heavily innervated by both extrinsic and intrinsic enteric nerves. Both extrinsic and intrinsic afferent neurons respond to various mechanical and chemical stimuli, but sensory nerve endings do not extend into the gut lumen. Instead they are separated from the luminal contents by a continuous lining of epithelial cells, which prevent their direct exposure to gut contents. It has been proposed that enteric sensory neurons indirectly receive their enteric information through hormones released from enteroendocrine cells. Gastrointestinal hormones like CCK, GLP-1 and PYY can directly stimulate vagal sensory neurons through hormone receptors on vagus nerve endings [24]. Interestingly, the communication between enteroendocrine cells and nerves appears to be bidirectional since enteroendocrine cell activity can be directly modulated by enteric neuron input. For example, vagal nerve stimulation can directly cause PYY hormone release from the small intestine [25, 26].

The traditionally held belief is that enteroendocrine cells communicate information from the intestine to other organ systems by the release of hormones into the blood. Although this has been established for some GI hormones, this view has now been challenged for others. For example, GLP-1 which is synthesized in the distal small intestine and colon is potentially inactivated by the proteolytic enzyme dipeptidyl peptidase-4 (DPP-4) and further inactivated in the liver so that by the time it reaches the arterial circulation, its concentration is so low that it may not be sufficient to activate islet cell GLP-1 receptors [27, 28]. This observation has raised serious doubts about the endocrine model of GLP-1 and suggested that most of the physiological functions of GLP-1 secreted from enteroendocrine cells may be mediated through direct activation of enteric sensory nerve endings [29].

This finding also raises the possibility that enteroendocrine cells have another way of relaying their sensory information. Recently, both a structural and functional connection has been described between enteroendocrine cells and enteric neurons [30]. This connection was discovered following the initial observation that some enteroendocrine cells possess basal processes that reach to other cells [31–33]. Using serial block face scanning electron microscopy (SBEM), it was shown that this process contained over 70% of the peptide-secreting vesicles in the enteroendocrine cell, abundant mitochondria, and neurofilaments which are typical structural proteins within axons [34]. This axon-like process was called a neuropod. In addition to neurofilaments, enteroendocrine cells were also found to be rich in other neuronal features including a number of pre- and post-synaptic genes [30]. Using immunofluorescence staining, it was shown that over 90% of PYY cells expressed the presynaptic marker synapsin 1 and 35% expressed postsynaptic markers like PSD95 [30]. These neuronal and synaptic features of enteroendocrine cells are consistent with previous findings that in addition to possessing hormone-containing large dense-core vesicles, enteroendocrine cells also have small clear synaptic vesicles [35]. These neuronal features of enteroendocrine cells highlight the potential for enteroendocrine cells to engage in both

afferent and efferent synaptic transmission. Indeed, through immunofluorescence staining, it was shown that enteroendocrine cells frequently connect with nerve endings [30, 36]. For example, in the colon, it was shown that nearly 70% of PYY cells connected with PGP9.5-positive nerves [30]. Interestingly, the connection between enteroendocrine cells and enteric nerves was recapitulated using *in vitro* culture and time-lapse recording [30]. In addition to the structural connection between enteroendocrine cells and the enteric nervous system, a functional synaptic connection was also evident. Using an *in vivo* retrograde rabies virus tracing system in a PYY-cre-rabG mouse model, it was shown that enteroendocrine cells are synaptically connected to efferent neurons [30]. The model of afferent and efferent innervation of enteroendocrine cells is shown in Figure 1.

Surprisingly, using SBEM it was shown that enteroendocrine cells also connect with enteric glia which nourish and protect enteric neurons [34]. It appears that glia may also secrete certain growth factors that promote the formation of the enteroendocrine cell's neuropod [34]. The enteroendocrine cell-neuron connection together with the extensive enteric nervous system network which signals to the central nervous system have been called the "gut connectome" [4].

Implications of the gut connectome

Given the complexity of enteric information, the physical innervation of sensory enteroendocrine cells could provide the opportunity for precise temporal and spatial luminal signal transmission as well as real-time modulatory feedback of enteroendocrine cell function. We believe the gut connectome is essential for a number of gut functions.

1. *Modulating digestive tract motility.* Serotonin in the gut is critical for gut motility [37]. Recent studies have shown that serotonin is contained in sub-groups of GIP, GLP-1 and secretin cells as well as in a high proportion of CCK cells [38]. Serotonin-containing cells can communicate directly with both enteric intrinsic and extrinsic afferent neurons. Previous studies have shown that serotonin can be released from enteroendocrine cells via noxious chemical stimuli via TRPA1 activation [39, 40]. Besides chemical stimuli, indigenous spore-forming bacteria from mouse and human microbiota also promote serotonin biosynthesis in colonic enteroendocrine cells [41]. Gene mutations within the serotonin biosynthetic pathway have been correlated with abnormal gut motility including irritable bowel syndrome (IBS) [42]. IBS is a group of disorders characterized by chronic abdominal pain and intestinal dysmotility (constipation or diarrhea) that occurs without discernable physical or anatomical abnormalities that would explain the symptoms. It is presumed that perturbation of the gut-brain axis accounts for the development of IBS [43]. Modification of the gut microbiota which increase colonic secretion has also been associated with IBS and it has been suggested that a change in luminal factors trigger abnormal hormone release from enteroendocrine cells [44–46]. It is possible that abnormal enteroendocrine activity perturbs the enteric nervous system and ascending signals to the brain via the vagus nerve [47]. Several studies have shown that changes in enteroendocrine hormone expression are associated with

improvement of IBS symptoms following dietary modifications [48]. Therefore, the enteroendocrine-enteric neuron connection may be a target for the treatment of IBS.

2. *Food perception and feeding behavior.* A key feature of the GI tract is its ability to integrate nutrient ingestion and digestion. This process is linked to sensations of hunger, eating and satiation, and is mediated by the gut connectome. One clear example is the connection of PYY/GLP-1 secreting cells with vagal afferent neurons [24]. PYY/GLP-1 cells possess receptors for fats, carbohydrates, protein and bile salts which enable them to receive a wide range of nutrient associated signals [49–51]. The connection of PYY/GLP-1 cells with vagal neurons allows the GI tract to transmit food-associated signals to the CNS to provide precise temporal and spatial mapping of nutrients within the gut. In addition to allowing the brain to monitor the nutrient status, information carried by the vagus nerve can project to the solitary tract of the nucleus, which can then be further integrated in the parabrachial complex and transmitted to forebrain regions including the hypothalamus and amygdala [52]. The hypothalamus is a well known “feeding” and “satiety” center and the amygdala is involved in reward-based behavior and emotions such as fear [53, 54]. Therefore, the gut connectome is critical for an organisms’ food sensing and behavioral response to food. In addition to central processing, the gut connectome is also linked to nutrient status and peripheral tissue metabolism either through direct vagal reflexes or neuronal output following CNS integration [55]. The peripheral tissue responses to nutrients include hepatic metabolism, insulin secretion and fat storage. Peripheral tissue metabolic status can also be perceived by vagal afferent neurons and in turn influence enteroendocrine cell function [25, 56]. Impairment of both peripheral tissue metabolism and food perception are critical to nutrient associated disorders like obesity. Restoring the food perception and gut signal transmission may provide a pathway for treating such disorders.
3. *Microbiota monitoring.* One prominent feature of the enteric luminal environment is its complicated eco-system composed of billions of microorganisms including bacteria, viruses, fungi and protozoa that have a profound impact on the host. The ability of microbes to influence behavior has been shown in a large number of studies, which have drawn great interest in understanding microbiota-brain communication [57]. It appears that microbiota in the gut are not only able to communicate with the brain and influence behavior but that the brain also communicates with gut microbiota to shape the microbial population for the benefit of the host[58]. In some instances, gut microbiota-brain communication requires immune activation, however, many commensal microbiota influence host behaviors in the absence of an immune response. For example, within hours of gut inoculation, *c. jejuni* produced an anxiety-like behavior in mice through a vagal-mediated pathway without immune activation [59, 60] demonstrating the existence of non-immune mechanisms that allow the brain to “see” and respond to microbes in the gut. It is likely that the gut connectome mediates such microbiota-brain communication. It is known that

innate immune sensors, such as TLRs play an important role in microbiota sensing [61]. TLRs can be activated by specific microbe-associated molecular patterns (MAMPs), that are specific to microbes. Certain TLRs are expressed in enteroendocrine cells and administration of TLR agonists like lipopolysaccharide (LPS) and synthetic bacteria lipoproteins stimulate secretion of gut hormones like CCK and serotonin [62–64]. Besides TLR-mediated microbiota sensing, enteroendocrine cells have also been shown to sense microbiota by their products. For example, short chain fatty acids (SCFAs) that are produced through microbial fermentation can directly stimulate secretion of GLP-1 and PYY from cells in the distal intestine through the activation of G-protein coupled receptors GPR41 and GPR43 [65, 66]. Besides commensal microbe sensing, food-borne pathogens can be cleared from the drosophila gut through TRPA1-dependent activation in enteroendocrine cells [67]. Even though the microbial sensors are also expressed in both extrinsic and intrinsic enteric afferent neurons [65, 68], the separation of enteric nerve endings from the gut lumen prevents afferent neurons from directly sensing microbes. However, enteroendocrine cells are ideally positioned to discern the composition and change in the microbiota community.

In addition to serving as a microbiota sensor, enteroendocrine cells may help shape the microbiota composition. Even though peptides are released from the basal surface of the enteroendocrine cell, recent studies have shown that serotonin can also be secreted into the intestinal lumen where it modulates bacterial growth and selection [41, 69, 70]. Therefore, it can be reasoned that at least part of the brain to microbiota communication may be mediated through enteric efferent innervation of enteroendocrine cells.

Conclusion

The body detects nutritional status with great precision through a highly integrated network of neural and hormonal signals that sense gut contents. This gut connectome provides a pathway for the gut to communicate with the brain and to respond to centrally processed neural information.

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Key points

- By virtue of their location in the intestinal epithelium and their connection to enteric nerves enteroendocrine cells act as sensory cells of the gut.
- The gut connectome regulates gastrointestinal motility.
- The body monitors nutrients and microbiota in the gut through the gut connectome.

Figure 1.

Gut connectome: built for gut sensing and signaling. Enteroendocrine cells reside in the intestinal epithelium with their apical surface oriented towards the lumen and secretory vesicles concentrated at the basal surface. Many enteroendocrine cells possess neuropods that are nurtured by glia and innervated by afferent and efferent nerves which allows them to send and receive neural signals. This connection provides a pathway for the gut to communicate sensory information. Figure adapted from [30].