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Review

Cholecystokinin and gut–brain signalling

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ABSTRACT

Enteroendocrine cells of the gastrointestinal tract act as a luminal surveillance system responding to either the presence or absence of food in the gut lumen. Collectively, their secretory products regulate the course of digestion and determine the delivery of nutrient to the gut by controlling food intake. Afferent neurons of the vagus nerve are an important target of gut hormones, particularly for control of food intake. The intestinal hormone cholecystokinin (CCK) stimulates vagal afferent neuron discharge and also controls the expression of both G-protein coupled receptors and peptide neurotransmitters in these neurons. When plasma CCK concentrations are low, for example in fasting, vagal afferent neurons express cannabinoid CB1 and melanin concentrating hormone (MCH)-1 receptors, both of which are associated with stimulation of food intake. Post-prandial release of CCK rapidly down-regulates the expression of both receptors but stimulates the expression of Y2 receptors in neurons projecting to the stomach. In fasting, there is also increased expression in these neurons of the appetite-stimulating neuropeptide transmitter MCH, and depressed expression of the satiety-peptide cocaine and amphetamine regulated transcript (CART). Secretion of CCK decreases expression of MCH and increases expression of CART. The neurochemical phenotype of vagal afferent neurons therefore encodes whether or not there has been nutrient ingestion over the previous period. At low plasma concentrations of CCK vagal afferent neurons exhibit increased capacity for appetite-stimulation, while post-prandial concentrations of CCK lead to enhanced capacity for satiety signalling. A gatekeeper function can therefore be attributed to CCK in that its presence or absence influences the capacity of vagal afferent neurons to respond to other neurohormonal signals.

Contents

1. Introduction

An impressive range of humoral factors signal changes in the luminal environment of the gastrointestinal tract [1]. The peptides and amines of the enteroendocrine cells (EECs) that act as primary transducers in luminal surveillance are secreted in response to either the presence, or absence, of luminal stimuli; they have been intensively studied for over a century. Taken together they can be thought to function in three loosely organised functional domains: the stomach, proximal small intestine and distal small intestine/colon. In each case, the secretory products of EECs ensure optimal digestion and absorption by controlling the nature of the luminal contents through stimulation or inhibition of digestive secretions, and by regulating the delivery of nutrient along the alimentary tract. In addition, it is now clear that there are many different immune modulators that respond to infection and inflammation in the gut wall and that act on some of the same targets as the products of EEC secretion. Quite recently, a range of lipid mediators has emerged that also act as gut signals, these include the cannabinoid (CB)1 agonist anandamide which stimulates food intake and the related

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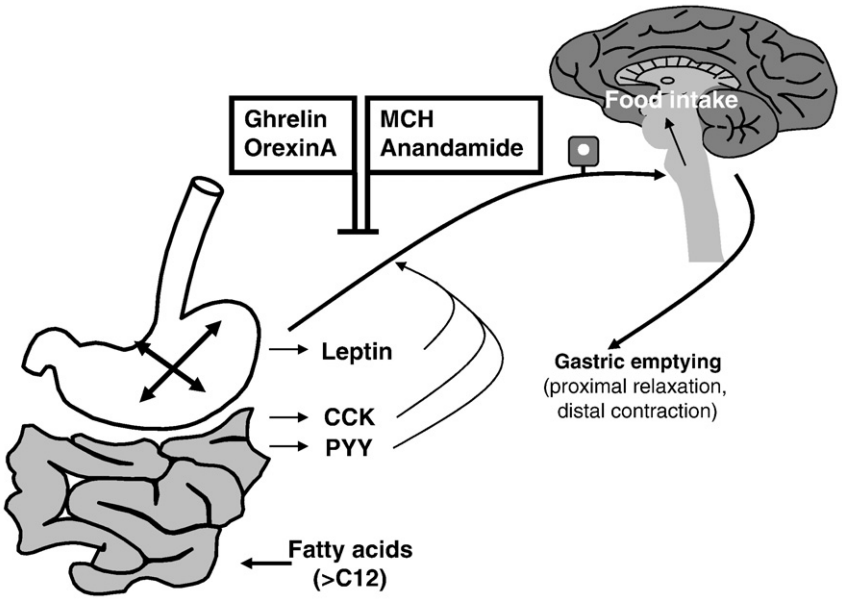

Fig. 1. Schematic representation of the neurohumoral factors acting on vagal afferent neurons. Leptin, CCK, PYY3-36 and GLP-1 are associated with stimulation of vagal afferent pathways leading to inhibition of food intake and, or, gastric emptying. Ghrelin, orexin-A, anandamide and MCH are associated with stimulation of food intake and, or, gastric emptying; CCK either inhibits expression of their receptors or they inhibit the actions of CCK.

oleylethanolamide which inhibits food intake [2,3]. Exactly how all of these signalling molecules are integrated is an important issue for present research.

Nutrient delivery to the small intestine is regulated by varying the rate of gastric emptying and through control of food intake. In the latter case, there are inhibitors of food intake from each of the functional domains mentioned above (stomach: leptin; small intestine: CCK; ileum/colon: PYY, GLP-1) (Fig. 1) and stimulants from two of them (stomach: ghrelin; small intestine: anandamide). The two stimulants are released when the gut is empty and the inhibitors are directly or indirectly released by luminal nutrients. In some circumstances gut hormones may act directly on CNS neurons after delivery in the circulation; however over the last decade or so, afferent neurons of the vagus nerve have emerged as important targets of gut hormones, particularly for control of food intake and gastric emptying. There have been many recent reviews of the literature on gut hormones and control of food intake [4–7]; the present account will focus on the relationships between gut endocrine signals and vagal afferent neurons with a special emphasis on CCK.

2. Integrative role of CCK in upper gastrointestinal tract physiology

Ingestion of fat or protein rich meals leads to secretion of CCK from I-type EECs of the upper small intestine. Both *in vivo* and in cultured STC1 cells, fatty acids with a chain length greater than 12 carbons are effective releasers of CCK while those with a chain length <10 C are largely ineffective [8,9]. In human volunteers, a rise in plasma CCK concentrations of 3–4 pM can be achieved with modest loads of C12 and is sufficient to inhibit gastric emptying and decrease the intake of a liquid test meal [10]. In addition to luminal nutrients, it is now clear that there is also elevated plasma CCK in humans infected with small intestinal pathogens such as *Giardia* [11]. Moreover, in a mouse model of intestinal inflammation due to infection with the nematode *Trichinella spiralis*, the secretion of CCK was shown to be dependent on CD4+ T-cells, via the release of IL-4 and IL-13 [12].

The primary actions of CCK are stimulation of pancreatic enzyme secretion and gall bladder contraction, and inhibition of gastric emptying and food intake. Collectively, these actions allow optimal digestion of fat and protein in the small intestine by balancing the capacity to secrete enzyme and bile salt with the delivery of nutrient substrates. Although there are direct actions of CCK on pancreatic acinar cells and on gastric smooth muscle cells, it appears that afferent neurons of the vagus nerve are a target of CCK for reflex stimulation of pancreatic secretion and inhibition of gastric emptying [13,14]. The same afferent pathway is thought to mediate the action of CCK in inhibiting food intake [15]. Many studies have confirmed the observation of Moran et al. who demonstrated that vagal afferent neurons express CCK1 (or CCK-A) receptors and that these are transported towards the periphery [16]. In addition to stimulation of vagal afferent nerve discharge CCK also controls the expression of both G-protein coupled receptors and peptide neurotransmitters involved in controlling food intake thereby regulating the capacity of other neurohumoral agents to act on this pathway.

3. The neurochemical phenotype of vagal afferent neurons

A wide range of receptors and neuropeptides have been shown to be expressed by vagal afferent neurons [6,17]. Work by Zhang et al. established that the neurochemical phenotype of vagal afferent neurons could be varied depending on experimental treatment. They showed that vagotomy decreased CCK1 receptor expression but increased expression of CCK2 (gastrin/CCK-B) and Y2 receptors [18]; they also showed that vagotomy influenced the expression of genes encoding the regulatory peptides galanin, NPY, VIP and CCK itself, which normally exhibit low or moderate levels of expression [19,20]. Subsequently it has become clear that the neurochemical phenotype of these neurons exhibits reversible changes in response to energy restriction.

In rats, withdrawal of food for periods of over 6 h has been shown to produce changes in both receptor and neuropeptide gene expression in vagal afferent neurons [21–25]. It is possible to identify three different patterns of gene expression following manipulation of energy intake. (a) There are some genes that exhibit broadly similar levels of expression in nodose ganglion neurons in rats that are fed *ad libitum* or fasted up to 48 h (Fig. 2). For example, the expression of CCK1, orexin type-1 (Ox-R1) and ghrelin receptors (GHS-1) seems not to be substantially altered with food withdrawal [20,21,26]. (b) Some