Cholecystokinin and gut–brain signalling

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A B S T R A C T

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.

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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...
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 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 CCK 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-R1) seems not to be substantially altered with food withdrawal [20,21,26]. (b) Some
genes exhibit increased expression in nodose ganglion neurons in rats following food withdrawal; examples of this class include the cannabinoid (CB)1 and melanin concentrating hormone (MCH)1 receptors and MCH itself; each of these is associated with orexigenic signalling in the CNS. (c) A third group exhibits depressed expression in fasted rats and is increased by refeeding eg cocaine and amphetamine regulated transcript (CART) and Y2 receptors both of which are associated with satiety signalling [21–23,25]. Refeeding of fasted rats reverses the neurochemical phenotype relatively rapidly [21–23,25,26]. The neurochemical phenotype of vagal afferent neurons exhibits, therefore, a simple form of memory by encoding whether or not there has been nutrient ingestion over the previous period (Fig. 3).

4. The gatekeeper functions of CCK on vagal afferent neurons

It is well established that CCK stimulates the discharge of vagal afferent neurons and increases intracellular calcium concentrations [27–29]. In addition, though, recent work has identified changes in gene expression dependent on the presence or absence of CCK. Administration of CCK to fasted rats stimulates expression of CART and Y2 receptors, and inhibits expression of CB1, MCH1 and MCH [21–23,25]. The effects seen with refeeding of fasted rats on expression of CB1, MCH1 and Y2 receptors, and on the neuropeptides MCH and CART, are attributable to the action of endogenous CCK since in each case they are blocked by the administration of a CCK1 receptor antagonist [21–23].

In cultured vagal afferent neurons, the neurochemical plasticity seen in vivo can be replicated by culturing in media either with or without fetal calf serum (FCS). For example, in full media (10% FCS) there is expression of CART but not MCH, while in serum-free medium there is expression of MCH but not CART [23]. Addition of CCK to neurons in serum-free medium rapidly restores CART expression and decreases MCH expression. The action of CCK in stimulating CART depends on activation of PKC, phosphorylation of CREB and activation of MAP kinase. The mechanisms of down-regulation are less clear, but neurons expressing a CREB inhibitor, seem not to demonstrate down-regulation of MCH suggesting that CREB is on both the stimulatory and inhibitor pathways downstream of CCK [23].
The actions of CCK in controlling Y2 receptor expression are interesting. When rats are fasted there is a progressive loss of expression of Y2 receptors with a $t_{1/2}$ of about 12 h. However, even after 48 h of food withdrawal there is a small population of neurons in which expression is preserved that amounts to 5–10% of the total population in the mid and caudal regions of the nodose ganglion. Studies combining retrograding tracing with immunohistochemistry have shown that the neurons exhibiting loss of Y2 receptors with food restriction mostly project to the stomach, whereas the vagal afferent neurons serving the ileum and colon continue to express these receptors during food withdrawal. The endogenous ligand of Y2 receptors is PYY3-36 produced by secretion of PYY from EECs predominantly located in the ileum and colon. The vagal afferent neurons projecting to these regions are therefore expected to be exposed to locally high concentrations of PYY3-36, and receptor activation is not dependent on CCK, while those to the stomach presumably respond to PYY3-36 delivered as a hormone in the circulation and signalling is subject to prior stimulation of receptor expression by CCK. It is worth noting that the action of PYY3-36 both in delaying gastric emptying and in stimulating fos expression in brain stem neurons (which is a putative marker of vagal afferent excitation) is CCK-dependent [25,30]; these observations are therefore consistent with the role of CCK in controlling Y2 receptor expression in vagal afferent neurons serving the stomach.

Together, these data indicate that CCK is able to switch the neurochemical phenotype of vagal afferent neurons between two states. At low plasma concentrations (through energy restriction), the vagal afferent pathway exhibits increased capacity for appetite-stimulation, while post-prandial concentrations of CCK lead to enhanced capacity for satiety signalling. Thus a gatekeeper function can be ascribed to CCK in so far as its presence or absence influences the capacity for responding to other neurohormonal signals.

5. Modulating the gatekeeper function of CCK

The action of CCK in stimulating vagal afferent neuron discharge and inhibiting food intake is potentiated by gastric distension, leptin and urocortin [28,29,31–34]. In contrast, orexin-A and ghrelin inhibit the action of CCK on these neurons [35,36]. During the immediate post-prandial period when CCK concentrations are rising and ghrelin concentrations are falling, vagal afferent neurons are exposed to both and interactions between the two are therefore possible. Although in principle the peptide obestatin derived from the ghrelin precursor is also likely to be secreted alongside ghrelin, recent work suggests it has no effect on CCK-satiety signalling [37]. The action of CCK in down-regulating CB1, MCH1 and MCH is inhibited by prior administration of ghrelin [26]; similarly, CCK-stimulated increases in CART and Y2 receptor expression are blocked by ghrelin administration [23]. In cultured vagal afferent neurons, ghrelin has been shown to act by excluding phoshoCREB from the nucleus [23]. The cellular mechanisms are unknown but merit further study.

6. Overview

Vagal afferent neurons seem able to adopt two states: one associated with expression of signalling molecules associated with inhibition of food intake, the other with signalling molecules associated with stimulation of food intake. These states are determined by energy intake over the previous day or so. In addition to the acute actions of CCK on vagal afferent neurons, it seems that there are
also longer term effects over hours or even days in which CCK switches neurons between the two states. Manipulation of these states could provide a novel therapeutic target for the control of food intake and the treatment of obesity.

References


