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Mechanisms of CCK signaling from gut to brain

Helen E Raybould, PhD

Department of Anatomy, Physiology and Cell Biology, UC Davis School of Veterinary Medicine, Davis, CA 95616, USA

Summary

Following the observation that exogenous peripheral injection of CCK could inhibit food intake, the mechanisms by which CCK influences the gut-brain pathway has been the subject of intense study for nearly thirty years. Recently, it has become evident that the system is more complex and that the consequences of CCK's action on the gut-brain pathway are more far reaching than previously recognized. This review will examine the recent evidence showing the role of CCK and CCK1Rs in modulating expression of other receptors for orexigenic and anorexigenic regulatory peptides at the level of vagal afferent neurons. In addition, new evidence showing the importance of the action of CCK at the level of the vagus nerve in the regulation of food intake, body weight and in activation of an anti-inflammatory pathway will be reviewed.

Introduction

Cholecystokinin (CCK) is secreted from endocrine cells that are concentrated in the proximal small intestine, but found throughout the length of the small intestine. The postprandial release of CCK is key in the activation of intestinal feedback control of gastrointestinal function, comprising short term inhibition of gastric emptying and acid secretion, stimulation of the exocrine pancreas and gall bladder, and inhibition of food intake. In this way, CCK plays a key role in coordinating the entry of nutrients into the small intestine with its digestive and absorptive capacity (1). There is good evidence that the majority of CCK-mediated intestinal feedback is mediated by activation of extrinsic neural pathways, specifically the vagal afferent pathway. Vagal afferents express CCK1Rs; the peripheral terminals of these afferent neurons lie in the wall of the GI tract, both in the mucosal and muscle layers. Within the mucosa, vagal afferents terminate within the lamina propria in close apposition to the basolateral membrane of entero-endocrine (EC) cells (2). This forms the anatomical basis for the hypothesis that release of regulatory hormones from endocrine cells, such as CCK, results in subsequent activation of vagal afferent terminals by a paracrine mode of action (3). Exogenous administration of CCK initiates action potentials in vagal afferent nerve fibers via CCK1 receptors; inhibition of gastric emptying, gastric acid secretion and stimulation of pancreatic exocrine secretion are mediated via this CCK1R-dependent vagal afferent pathway. In addition, CCK acting via a vagal afferent pathway inhibits food intake as part of the response to food in the proximal gut (4).

The use of specific and potent receptor antagonists, such as devazepide and loxiglumide, have demonstrated the role of endogenous CCK in mediating the inhibition of gastric emptying,

Address for correspondence: Helen E Raybould, Vet Med: APC, 1321 Haring Hall, Davis, CA 95616, USA, Tel: 530 754 6555, FAX: 530 752 7690, E-mail: heraybould@ucdavis.edu.

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gastric acid secretion and food intake in response of fat and protein, but not carbohydrate, in the intestine (5). While the majority of these studies have been performed in rodents, a number of studies have confirmed these findings in non-human primates. Importantly, a number of studies have shown that CCK and the CCK1R mediate inhibition of gastric function, food intake and satiation in response to intestinal nutrients in humans (6,7).

This aim of this article is to review some of the newer concepts concerning the role of CCK and the gut-brain axis. There is compelling evidence that CCK interacts with other regulatory peptides at the level of receptor expression and function of the vagal afferent pathway which may play an important role in the regulation of food intake and body weight. In the addition, the role of the vagal afferent and CCK1R pathway in activation of an anti-inflammatory pathway will be discussed.

CCK and the regulation food intake

CCK has received considerable attention with respect to short term regulation of food intake. Administration of CCK induces satiation, the process by which a meal is terminated, leading to a reduction in meal size. In rodents, exogenous CCK or perfusion of the small intestine with nutrients, such as protein or fat, terminates feeding and administration of CCK1 receptor antagonists will reverse these effects.

Despite the evidence that CCK plays a role in the regulation of postprandial GI function and food intake, CCK1 receptor deficient mice have a remarkably normal phenotype (8,9,•10). These mice have identical growth curves and overall daily food intake as wildtype mice. This would seem to suggest that CCK plays little if any role in satiety, the response regulating meal interval and meal frequency, or in overall regulation of body weight. As predicted, CCK1R null mice show no inhibition of food intake or gastric emptying, or activation of neurons in the NTS, the region in the brainstem where vagal afferent neurons terminate, in response to exogenous CCK (11). Alterations in gallbladder function have been documented in these mice; gall bladder volumes were larger and there is altered cholesterol absorption and increased susceptibility to develop gallstones when mice were maintained on an atherogenic diet (12).

However, it is clear that there is a deficit in the postprandial regulation of GI function in these mice. Activation of the vagal afferent pathway in response to intestinal lipid, using immunocytochemical detection of fos protein as a marker of neuronal activation of second order neurons in the NTS, was markedly reduced in CCK1R null mice compared to wildtype controls (11). Intestinal lipid-induced inhibition of meal-stimulated gastric acid secretion was completely abolished in the CCK1R null mice. Inhibition of gastric emptying in response to dietary lipid in the diet was reduced by around 50%. The mediator involved in the residual response to intestinal lipid remains to be identified, but could be PYY or GLP-1; both are released from L cells in the distal small intestine in response to fat and inhibit gastric emptying.

Although there was no change in overall daily food intake, a thorough analysis of food intake in these mice revealed that meal patterns were significantly changed. CCK1R null mice eat significantly longer and larger meals compared to wildtype mice, but meal frequency was reduced, leading to no overall change in daily food intake (•13). This reduction in satiation was more marked when mice were ingesting a high fat, high energy diet. This finding is consistent with diminished detection of dietary lipid in the small intestine leading to altered meal patterns, but other factors that regulate meal patterns over the longer term, such as leptin or insulin, are able to maintain normal daily food intake and normal body weight. These findings confirm that CCK is required for regulation of caloric intake within a meal, but that other factors are involved for regulation over multiple meals.

However, there is evidence that CCK interacts with long-term signals of energy balance; this interaction occurs at the level of the hypothalamus and recent evidence suggests that an important component of this interaction occurs at the level of the vagus nerve.

Interaction of vagal CCK1Rs with other factors controlling food intake

Leptin is released from adipocytes and circulating leptin plays an important role in the central regulation of food intake and energy balance (14). Leptin acting in the hypothalamus enhances the sensitivity to short term satiety signals, such as CCK. However, the stomach also secretes leptin and leptin receptors (Ob-R) are expressed by vagal afferent neurons, thus providing the possibility that leptin is involved in peripheral regulation of food intake by acting on vagal afferent terminals within the GI tract. Leptin receptors are co-expressed with CCK1R on vagal afferents and the excitatory response of vagal afferents to exogenous CCK is enhanced by co-administration of leptin (15). In addition, functional responses to exogenous CCK are modulated by leptin; in rodents, inhibition of gastric emptying and food intake in response to exogenous administration of CCK is enhanced by leptin (16). Expression of the leptin receptor by vagal afferent neurons is not static but is increased by fasting and decreased by refeeding; these changes occur quite rapidly, within 2 hours of refeeding (18,19).

This interaction between long term and short term satiety factors and also between regulatory peptides that are orexigenic or anorexigenic at the level of vagal afferents may be more extensive than previously recognized. The vagus nerve expresses receptors for many of the regulatory peptides that are released from the intestinal wall, pancreas and from adipocytes and shown to influence both short and long term food intake. Thus, the vagus nerve expresses receptors for orexigenic peptides such as ghrelin (20), orexin (OX-1R) (21) and cannabinoids (CB1) (••22) and also for anorexigenic peptides, including PYY (23), GLP-1/GLP-2 (24,25), in addition to CCK and leptin. Similarly to the leptin receptor, the level of expression of these receptors can be altered by the fed status of the animal, a response that is dependent on CCK1 receptors. In addition, evidence is beginning to emerge for functional interaction of these different receptors.

The majority of nodose neurons that express CCK1Rs also express receptors for ghrelin, orexin, cannabinoids (CB1) and leptin. The expression of CB1 receptors on vagal afferents, both at the RNA and protein level, is increased by fasting; refeeding or exogenous CCK treatment of fasted rats decreased the expression of CB1Rs and this response was blocked by prior administration of a CCK1R antagonist (22). Thus, after eating when CCK levels are high, CCK acts to decrease expression of a receptor associated with stimulation of appetite. This suggests that CCK may be involved not only in the termination of meals but also in the functional expression of orexigenic signals by decreasing the level of receptor expression on vagal afferents.

The receptor for ghrelin, a peptide found in endocrine cells in the gastric corpus and associated with stimulation of appetite, is also expressed in nodose neurons expressing the CCK1R. Ghrelin had no effect on the expression of the CB-1 receptor but inhibited the CCK1R-dependent decrease in CB-1 receptor abundance produced by feeding (26). Therefore, ghrelin may inhibit the down regulation of orexigenic signals produced by feeding, thus adding to its ability to increase food intake (•27,28).

Data from a study of meal patterns in CCK1R null mice provides a possible functional correlate of these morphological findings and also provide evidence that the CCK1R may be involved not only in intrameal satiation but also in meal initiation (13). After a short fast, CCK1R null mice eating the high fat, high energy diet have a significantly shorter latency to the start of the first meal. This decrease in the time to the first meal may correspond to increased “hunger” in these mice. The mechanism is unclear, but may involve modulation of the response to other

regulatory peptides involved in control of food intake. This suggests that CCK1R deficient mice may have a deficit not only in the mechanism by which food in the gut lumen initiates satiation and reduced short term food intake, but that these mice may indeed be more “hungry”. It was of interest to note that this decreased time to meal initiation occurred when mice were ingesting rodent chow, but was more marked when mice were feeding high fat, high energy food. It is interesting to speculate that in the absence of CCK1R expression by vagal afferents, there is an altered expression of other receptors, such as an increased expression of cannabinoid or ghrelin receptors, as predicted from the studies described above.

The relevance of these findings is unclear, but to speculate, it has been found that, when rats are maintained on high fat diets, there is a decrease in the response of the vagal afferent pathway to the satiating effects of CCK and in the ability of CCK to activate that vagal afferent pathway (•29,30). In this respect, maybe the CCK1R null mice represent an extreme of individuals eating a high fat, high energy diet, where because of a downregulation of CCK1Rs in vagal afferents, there is no longer a balance between the orexigenic and anorexigenic signals arising from the periphery. In this respect, maybe CCK1R is important in determining the “sensitivity” to other peripherally-acting regulatory peptides involved in the control of food intake.

In addition to the interaction between CCK1 receptors and ghrelin and cannabinoid receptors, evidence is beginning to emerge for an interaction between CCK and other anorexigenic peptides, such as PYY3–36. Exogenous administration of PYY3–36 activates the vagal afferent pathway; this pathway mediates the effects of PYY3–36 on gastric emptying but not food intake, which is more likely via a direct effect on neurons in the hypothalamus (31). Administration of the CCK1R antagonist devazepide produced a significant attenuation of PYY3–36 induced activation of the vagal afferent pathway and inhibition of gastric emptying. This suggests that functional responses to PYY3–36, mediated at the level of the vagus nerve, are partly dependent on the expression of CCK1Rs. There is also evidence for an synergistic interaction between PYY3–36 and GLP-1 (•32).

CCK1Rs and the vagal anti-inflammatory pathway

Although CCK and the gut-brain pathway in the control of food intake and its possible role in regulation of body weight, has gained considerable attention over the last few years, another possible consequence of lipid-induced activation of the vagal afferent pathway is in control of inflammation, via activation of the cholinergic anti-inflammatory pathway.

It is well recognized that the production of anti-inflammatory cytokines are crucial in the response of the body to limit and balance the effects of inflammatory cytokines. Recently, Tracey and co-workers have characterized a vagal, cholinergic anti-inflammatory pathway (33). This group demonstrated that electrical stimulation of the vagus nerve inhibits the release of the inflammatory cytokine TNF α released in a model of experimental sepsis induced by lipopolysaccharide (LPS) injection (••34). Furthermore, vagal activation inhibits cytokine release and also improves the disease endpoints in experimental sepsis, ileus, hemorrhagic shock, pancreatitis and a number of other inflammatory models. This inhibition is mediated via the vagal, cholinergic nicotinic efferent innervation of macrophages in the subdiaphragmatic viscera, primarily the spleen and liver.

Further, it was shown that dietary fat strongly reduced systemic inflammation after hemorrhagic shock, suggesting an interaction between macronutrients and a systemic immune response (35). Luyer et al hypothesized that enteral fat acts as a stimulant of parasympathetic outflow via the afferent vagus nerve leading to activation of this anti-inflammatory vagal reflex pathway. Thus, they found that feeding rats high fat food prior to induction of hemorrhagic shock reduced release of TNF α and IL-6 compared to rats that were fasted or given low fat food. Administration of a CCK1R antagonist reversed this anti-inflammatory response to

enteral fat (••36). Along with the ability to modify the release of inflammatory cytokines, enteral fat also help to maintain intestinal barrier function and reduce translocation of bacterial products across the gut wall.

This role for vagal CCK1Rs in mediating an anti-inflammatory pathway is by itself an important clinical observation that challenges the accepted dogma of fasting patients prior to and immediately after surgery. However, in light of observations described above on the dynamic regulation of receptors expression by the vagus nerve, and the possible role of long term increased in dietary fat in this regulation, it is important to determine how long term changes in receptor expression by vagal afferents may alter visceral function in a number of pathological situations, such as inflammatory bowel disease, metabolic syndrome and obesity.

Conclusions

The last few years of research on CCK has confirmed many previous observations on the role of CCK and the vagus nerve in the control of gastrointestinal function and food intake, but also revealed some emerging and exciting areas of research. The implications of the dynamic expression of receptors for regulatory peptides by the afferent vagus nerve are not fully understood but provide a fruitful avenue of research to increase our understanding of the role of the autonomic nervous system in the maintenance of homeostasis.

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