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Intestinal feedback signaling and satiety

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ABSTRACT

Peptidergic and neural signals arising from the presence of food in the gastrointestinal track provide feedback signals to the brain about the nature and quantity of consumed nutrients. Peptide secreting cells are differentially distributed along the gastrointestinal tract. How ingested nutrients activate or inhibit peptide secretion is complex and depends upon local, hormonal and neural mechanisms. The mode of action of the various peptides is equally complex involving endocrine, paracrine and neurocrine signaling. The success of bariatric surgical approaches to obesity treatment is secondary to alterations in gastrointestinal feedback signaling and roles of increased secretion of lower gut peptides such as peptide YY (PYY) and glucagon like peptide 1 (GLP-1) in mediating the superior effects of Roux-en-Y gastric bypass (RYGB) surgery are becoming evident. Direct nutrient delivery to jejunal sites that models the site of gastric-jejunal anastamosis in RYGB is especially effective at inhibiting food intake. Such infusions also stimulate the release of lower gut peptides suggesting a role for increased gut peptide signaling in sustaining such feeding inhibitions. Thus, gut peptides are clear targets for future obesity therapeutic developments.

1. Introduction

Nutrients in the gastrointestinal tract stimulate a variety of signals that provide feedback to the brain about both their quality and quantity. Such signals are critically important to the controls of food intake, especially the controls of meal size. This is most dramatically demonstrated in what is referred to as sham feeding. Sham feeding paradigms take a number of forms but what they share in common is that ingested food drains out preventing its accumulation in the stomach or its entry into the intestine. In the sham feeding situation, significantly more is consumed than in the normal feeding situation — normal meal termination does not occur [1]. The absence of signals arising from both the stomach and the intestine can be demonstrated to play a role in this over-ingestion but the major source of such inhibitory feedback appears to arise from the intestine. For example, infusion of a liquid food into the proximal intestine significantly inhibits sham feeding and can be shown to elicit a normal sequence of satiety [2,3]. Thus, signals arising from the presence of food in the intestine appear to be sufficient for terminating a meal.

Nutrients in the stomach provide feedback in relation to their volume. Nutrient loads isolated to the stomach with the use of a pyloric noose inhibit food intake. With a closed pyloric noose different gastric volumes reduced food intake in a dose dependent manner according to their volume [4]. Altering the concentration or nutrient character of the gastric loads did not differentially affect food intake [4]. Gastric nutrients also activate vagal afferent fibers innervating the stomach in relation to their total volume — altering their concentration does not affect vagal afferent activity [5].

The nature of the inhibitory signals arising from the intestine is more complex. Vagal afferents innervating intestinal sites do respond to the local volume or stretch of the intestinal wall, but the activity is also responsive to the nutrient character or concentration [6,7]. Furthermore, the intestine is not homogenous. Differential nutrient absorption occurs in various segments and enteroendocrine cells are differentially distributed along its length. In this review, we will provide a characterization of the peptide feedback that plays various roles in feeding control and discuss data that supports the idea that nutrients delivered to various intestinal sites may differentially affect food intake and this may be the result of differential peptide secretion.

The gastrointestinal tract secretes a variety of peptides that play roles in stimulating and inhibiting food intake. Three different, but in some cases overlapping, actions can be identified: feeding stimulation, feeding inhibition specific to the meal that stimulated the release and feeding inhibition that can go across multiple meals by altering inter-meal intervals and/or by suppressing the size of subsequent meals. The site of release and patterns of secretion are consistent with the actions of these peptides.

2. Meal initiation

Ghrelin is a gastric peptide released from oxyntic cells in the stomach [8]. Plasma levels of ghrelin rise prior to meals and rapidly decline when food is consumed [9]. Exogenous ghrelin administration increases food intake [10] and ghrelin is thought to play a role in meal

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initiation. Examinations of meal patterns in response to ghrelin administration have demonstrated major effects on meal number with smaller effects on the size of spontaneous meals [11]. Central and peripheral ghrelin administration results in increased expression of the orexigenic peptides NPY and AgRP within the hypothalamic arcuate nucleus suggesting a common final pathway for the feeding stimulatory effects [12,13]. Ghrelin transport across the blood brain barrier has been demonstrated suggesting that such hypothalamic sites may be directly sensing alterations in plasma ghrelin levels [14]. These sites do contain ghrelin receptors [15].

In addition to a hypothalamic mode of action for ghrelin, the brainstem also has been suggested to play a role. Ghrelin receptors are also expressed by extra-hypothalamic cells including those of the dorsal vagal complex [16]. Central and peripheral administration of ghrelin activates cells in the nucleus of the solitary tract and area postrema as indicated by an increase in the number of c-fos positive cells [17] (Hirofumi, Hiroaki et al.). Administration of ghrelin in the fourth ventricle or directly in the dorsal vagal complex results in a hyperphagic response with a magnitude similar to the one obtained after injection into the third ventricle [11]. The ability of peripheral and central injections of ghrelin into the forebrain or brainstem to stimulate food intake and increase arcuate NPY mRNA expression suggests a distributed ghrelin system that mediates changes in food intake through a final common output involving the arcuate nucleus [13].

The controls of ghrelin secretion are not completely understood. Although ghrelin is primarily a gastric peptide, the drop in ghrelin secretion in response to food intake depends upon ingested food gaining access to intestinal sites. Food localized to the stomach is not a sufficient stimulus for decreasing ghrelin secretion [18]. Furthermore, jejunal and duodenal nutrient infusions are equally effective at reducing ghrelin secretion suggesting an indirect control that may be neurally or hormonally mediated [19]. Vagotomy experiments have demonstrated that intact vagal signaling is not necessary for the meal-induced decline in ghrelin secretion but that the rise with food deprivation does depend on the vagus [20]. Glucose and amino acids have been shown to be equally effective in inhibiting ghrelin release while lipids are less effective [19]. The role of other gut peptides in the meal-induced decrease in circulating ghrelin has not been thoroughly investigated. However, a postprandial rise in insulin does not appear to be a necessary signal since plasma ghrelin levels also fall in response to nutrients that do not elevate insulin and in response to a meal in type 1 diabetics lacking insulin [21]. A role for cholecystokinin (CCK) in the ability of lipids to inhibit plasma ghrelin levels has been demonstrated. Thus, administration of the CCK1 antagonist dexloxiglumide blocks the ability of intraduodenal long chain fatty acids to inhibit ghrelin levels [22]. Consistent with these data, administration of amounts of CCK that raise plasma levels equivalent to those found post-prandially also result in a decline in plasma ghrelin levels [23]. Whether the release of other intestinal peptides contributes to the meal-induced decrease in plasma ghrelin levels has not been adequately investigated. As well as responding to current nutritional status, ghrelin levels are also affected by body weight. Ghrelin levels rise with weight loss and levels tend to be lower in obese than in lean individuals [9]. How levels of body fat affect ghrelin secretion is not well understood.

3. Within meal satiety signaling

Plasma levels of some peptides increase rapidly in response to food intake. Examples are cholecystokinin (CCK), amylin and glucagon. CCK is released from I cells mainly located in the proximal duodenum. Both amylin and glucagon are pancreatic peptides. Long chain fatty acids and proteins are particularly effective CCK secretagogues [24] although plasma CCK levels also rise in response to carbohydrate rich meals [25]. Amylin is co-secreted with insulin and levels rise rapidly in response to carbohydrate ingestion [26]. The ability of other macronutrients to stimulate amylin release is not well studied although given the relationship with insulin, it is likely that amylin secretion would also be stimulated by proteins and lipids although to a lesser extent than in response to carbohydrate ingestion. Although glucagon's main physiological role is to stimulate glucose production, plasma levels of pancreatic glucagon do rise in response to ingestion of mixed nutrient meals [27].

Meal contingent administration of each of these peptides has been demonstrated to reduce meal size and produce satiety [28–30]. Importantly, the actions are limited to that meal and do not affect subsequent food intake. Furthermore, the actions of the exogenously administered peptides mimic the actions of the endogenous peptides. For example, administration of CCK1 receptor antagonists increases food intake and do so by increasing the size of the meal [31,32]. Similarly, CCK1 receptor knockout mice or OLETF rats lacking CCK receptors have significantly increased meal sizes [33,34]. Similar actions have been demonstrated for an amylin antagonists and a glucagon antibody [35,36]. Administration of these compounds result in increased food intake expressed as increases in the size of meals.

The mode of signal transmission differs across peptides. In some cases the actions appear to be through local paracrine effects. For example, plasma levels may simply be a marker of peptide release having occurred. For CCK, plasma levels are unlikely to be the relevant signal [37]. CCK's satiety actions depend upon the interaction of the peptide with receptors on vagal afferent fibers [38]. Given the close proximity of intestinal I cells and vagal terminals in the intestinal villi, it is likely that such interaction is paracrine in nature and that plasma levels may not reflect levels at the critical site of interaction. Amylin's mode of action is endocrine. Amylin's feeding inhibitory effects depend upon interaction with amylin receptors within the area postrema, a dorsal hindbrain circumventricular organ with a porous blood brain barrier [39]. The satiety actions of pancreatic glucagon appear to depend upon its actions at the site innervated by the hepatic vagus [40]. As the hepatic branch innervates both the liver and proximal intestine either site remains a possibility.

4. Across meal satiety signaling

Peptide YY (PYY) and glucagon like peptide-1 (GLP-1) have demonstrated feedback roles in food intake and both are secreted from L cells in the distal intestine. Their pattern of secretion is different from that of CCK or amylin in that plasma levels can remain elevated for up to 6 h following meal termination. This pattern of release suggests roles for these peptides that extend beyond the meal that stimulated their release.

The controls of PYY and GLP-1 release differ even though they are secreted from the same enteroendocrine cells. Plasma PYY levels are significantly increased within 15 min of meal ingestion and remain elevated for a number of hours [41]. PYY release is stimulated both by nutrients directly contacting lower intestinal L cells and in response to duodenal lipids [42]. Duodenal nutrients most likely contribute to the early release and this is both hormonally and neurally mediated [43]. CCK has been demonstrated to play a role in the release of PYY as exogenous CCK increases plasma PYY levels [23] and administration of a CCK antagonist blocks the ability of duodenal lipid to stimulate a PYY release [22]. Distal intestinal administration of a range of nutrients has been demonstrated to stimulate PYY release and it is this direct nutrient stimulated release that contributes to the duration of PYY elevation following a meal [44].

Within the intestinal L cells, proPYY is processed to PYY(1–36) with very little conversion to PYY (3–36) [45]. Once released into the circulation, PYY(1–36) is rapidly converted to PYY(3–36) through the enzymatic action of dipeptidyl peptidase-4 (DPP-1 V) [46]. PYY(1–36) and PYY(3–36) have different affinities for the various Y receptors [47]. PYY(1–36) has broad activity across multiple of the receptor