Review

Appetite signaling: From gut peptides and enteric nerves to brain

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Abstract

The signaling systems underlying eating behavior control are complex. The current review focuses on gastrointestinal (GI) signaling systems as physiological key functions for metabolic control. Many of the peptides that are involved in the regulation of food intake in the brain are also found in the enteric nervous system and enteroendocrine cells of the mucosa of the GI tract. The only identified hunger-driving signal from the GI tract is ghrelin, which is mainly found in the mucosa of the stomach. Neuropeptides in the brain that influence food intake, of which neuropeptide Y, agouti gene-related peptide and orexins are stimulatory, while melanocortins and α-melanocortin stimulating hormone are inhibitory, are influenced by peptide signaling from the gut. These effects may take place directly through action of gut peptide in the brain or through nervous signaling from the periphery to the brain. The criteria for considering a gut hormone or neurotransmitter in a satiety signal seem to be fulfilled for cholecystokinin, glucagon-like peptide-1 and peptide YY(3-36). Other endogenous gut signals do not fulfill these criteria as they do not increase food intake in knock-out animals or in response to receptor antagonism, or display an inconsistent temporal profile with satiety and termination of the meal. Satiety signals from the GI tract act through the arcuate nucleus of the hypothalamus and the solitary tract nucleus of the brain stem, where neuronal networks directly linked to hypothalamic centers for food intake and eating behavior are activated. We have primarily focused on GI effects of various gut peptides involved in the regulation of food intake, using motor activity as a biomarker for the understanding of gut peptide effects promoting satiety.

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1. Introduction

Energy balance is a metabolic state that exists when total body expenditure equals dietary energy intake. Normally, energy balance is very well regulated both in the short- and long-term. However, in some individuals there is an imbalance between energy intake and energy expenditure resulting in weight gain and, ultimately, obesity. Early research on obesity concentrated almost exclusively on hypothalamic control of food intake, where the maximum daily intake of food was determined by some limiting factor in addition to hypothalamic mechanisms [1]. Today it is recognized that short-term control of food intake involves not only the central nervous system (CNS), but also the adrenals, pancreas as well as gastrointestinal (GI) tract. Furthermore, adipose tissue has been found to play an important role in the long-term regulation of food intake by producing several endocrine and paracrine mediators, including leptin, adiponectin, resistin and tumour necrosis factor-α, which are known to influence food intake. Our understanding of factors regulating food intake has increased greatly during the last decade, partly as a result of the discovery of leptin [2]. That the study not only demonstrated that our fat stores can signal energy reserves to the CNS, but also spawned an increased interest in the field of appetite regulation. The resulting research has improved our knowledge of the signals underlying energy balance. The aim of this review is to further broaden the view of peripheral regulation of food intake by describing the influence of different gut peptides on appetite.

2. Gastrointestinal signaling

Many GI peptide hormones are connected to different food-related gastric and intestinal signals [3]. Distention of the stomach activates gastric stretch receptors and mechanoreceptors that transmit satiety signals to the brain [4]. The stomach also serves as a food reservoir, which ultimately delimits eating. However, this does not happen physiologically and a meal is usually terminated long before such stretch sensors are activated. This points in favor of some, yet undefined, metabolic signal contributing in the cessation of a meal. Even though the specific relationships between such gastric signals and release of GI peptides in relation to hunger and satiety have not been clearly identified, recent research on gut peptide hormones has shed some light on the importance of the GI tract in regulation of food intake (Fig. 1).

2.1. Hunger signal and meal initiation

Today the only GI peptide hormone with confirmed orexigenic properties is ghrelin [5]. Ghrelin, is a ligand for the growth hormone secretagogue receptor, and is produced mainly in the stomach (Fig. 1). When administered both centrally and peripherally it stimulates appetite and increases food intake in animals [6] and man [7]. Plasma ghrelin peaks before a regular meal, then decreases to progressively increase to another peak just before the next meal suggesting that ghrelin may be a meal initiator [8]. Ghrelin also seems to play a role in long-term regulation of energy balance as chronic administration of ghrelin in rodents results in hyperphagia and weight gain independent of growth hormone [6]. The effects of ghrelin on eating behavior are mediated via the arcuate nucleus and the solitary tract nucleus to merge in the hypothalamus. There is also data suggesting that ghrelin partly exerts its effect through vagal afferent loops [9]. There, ghrelin opposes the actions of leptin through disinhibition of second line neuropeptides such as neuropeptide Y (NPY) and agouti gene-related peptide (AgRP) [10]. Circulating levels of ghrelin are lower in obese than in normal-weight individuals [11], and negatively correlated with body mass index [12]. The increase in ghrelin during starvation boosts eating behavior and the low levels of ghrelin in obesity may be a secondary response to over-eating [11]. Indeed, ghrelin is negatively correlated with percentage body fat, fasting insulin, and fasting leptin, all of which

![Fig. 1. Afferent gastrointestinal signals controlling food intake.](image-url)
are elevated in obesity [11,12], indicating a regulatory role for ghrelin and the upper GI tract in control of food intake.

Like many of the peptides involved in the regulation of food intake ghrelin also influences GI motility. In rats, intravenous ghrelin increases fasting motility [13] and increases the rate of gastric emptying [14]. There are ghrelin receptors in the gut, which most likely mediate these effects of ghrelin on gut function [15]. These data, in addition to those demonstrating inhibitory effects of many gut peptides involved in satiety responses demonstrate a link between motor function in the gut and appetite regulation.

2.2. Satiety signals

Amongst the GI peptide hormones several are known to be anorexigenic, mainly cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide YY(3-36) (PYY(3-36)), which all are recognized as physiologic regulators of food intake (Fig. 1). CCK is the most studied gut peptide regulating control of food intake, and research on CCK has been widely reviewed [16]. After food intake, CCK is released into the circulation from endocrine L-cells of the duodenum and the jejunum [17]. Studies in several species, including humans have shown that CCK inhibits food intake [18,19], although a concurrent gastric preload is necessary to achieve a normal satiety effect with CCK in both obese and lean subjects [20]. Peripherally administered CCK also acts on CCK₁ (previously CCKA) receptors in the gastric antrum, known to be involved in the CCK-mediated inhibition of gastric emptying [21]. Hence, CCK₁ receptors are found in the abdominal part of the vagus nerve [22] and vagotomy eradicates the satiating effect of this peptide in rats. A relationship between decreased plasma levels of CCK, increased hunger and decreased fullness has also been reported in man [23], speaking in favor of CCK as a true physiological mediator of satiety.

GLP-1 and glucagon-like peptide-2 (GLP-2) are produced and secreted from endocrine L-cells in the mucosa of the ileum and colon. After a meal, both peptides are released in equimolar amounts to the blood stream [24,25]. GLP-1 is a major contributor to the ileal brake mechanism of the upper GI tract, thereby modulating gastric emptying and acid secretion [26]. GLP-1 also exerts dual actions in regulation of blood glucose concentrations through its concurrent insulinotropic and glucagonostatic actions [27]. Since GLP-1 slows gastric emptying of both liquid and solid meals [26,28], the metabolic requirements for insulin after food intake are reduced [29]. Accumulating evidence indicates that GLP-1 exerts its effects on GI functions through the vagus nerve both in animals and man [29–33].

After a meal GLP-1 also brings dual actions on feeding behavior and satiety into play: intracerebroventricular (ICV) injections of GLP-1 in rats inhibit food and water intake [34–36] and induce c-fos expression in the paraventricular nucleus of the hypothalamus [36]. ICV administration of the GLP-1 receptor antagonist exendin(9-39)amide also results in increased food intake in satiated, but not in fasted, rats [36]. With continuous ICV infusion exendin(9-39)amide rats not only increase their food intake, but also their body weight [37]. However, no effects were seen with intraperitoneal injections, suggesting central mechanisms to be involved in the satiety action of GLP-1. Furthermore, GLP-1 release in obese subjects has been found to be lower in obese than lean subjects [38–40]. In humans, studies invariably report decreased food intake with ratings of reduced hunger and increased fullness following infusion of GLP-1, including studies in normal weight, diabetic and obese participants [41–48].

In contrast to GLP-1, the role of GLP-2 in the regulation of food intake is unclear. GLP-2 is primarily known to exert trophic effects on the intestinal mucosa [49], which may lead to advances in the treatment of short bowel syndrome [50]. However, gastric emptying studies including ratings of satiety have failed to verify any effect of GLP-2 in appetite control in man [51], and peripheral administration of GLP-2 did not influence appetite and ad libitum food intake [52].

A third peptide from the pre-proglucagon gene has recently been implicated in regulating food intake in obese subjects. Oxyntomodulin (OXM), which is released from intestinal L-cells in response to food ingestion has been shown to reduce food intake. Subcutaneous injections of OXM over 4 weeks significantly reduced food intake and resulted in an additional 0.45 kg per week weight loss compared to a control group [53].

The truncated form of PYY, PYY(3-36), is released after a meal from the GI tract and induces satiety [54]. The effect of PYY(3-36) has been suggested to have a longer duration of action than other GI satiety peptides. Animal studies show that PYY(3-36) exerts its effect as a Y₂-receptor agonist, thereby suppressing NPY-induced hunger in the arcuate nucleus of the hypothalamus. In analogy to GLP-1, PYY concentrations in plasma after a meal have recently been shown to be lower in obese than lean subjects [55], which should reinforce the argument for PYY(3-36) as a mediator of satiety. However, as pointed out above, this property seems not to be specific but rather a common feature of the obese (cf. GLP-1); due to weak signaling from the gut inhibitory mechanisms on food intake. PYY(3-36) has also been shown to decrease food intake in rodents [54]; however, there is an ongoing debate regarding this, as other independent researchers have been unable to reproduce these results [56]. In analogy with other GI peptides involved in regulating food intake PYY also inhibits fasting small bowel motility [57] and gastric emptying [58] and there are suggestions that the anorectic effects of PYY(3-36) may be the result of nausea (Thelin, Näslund and Hellström, unpublished).

Very recently a second peptide has been isolated from the proghrelin gene. This peptide of 23 amino acids binds to the orphan G protein-coupled receptor GPR39 and has been named obestatin. Obestatin has been reported to suppress food intake, jejunal contractions in vitro and gastric emptying in vivo in mice [59]. However, as judged from work by our group and others the role of obestatin as a regulator of motility and appetite can be questioned. Further work is needed to characterize obestatin in detail, as well as its effects and relationship to ghrelin.

3. Signaling in obesity

Obese subjects in general have a larger than normal gastric capacity [60,61] (Fig. 2). The volume not only seems to be
important for satiety signaling but also intragastric pressure [60]. Delayed gastric emptying, due to gastric distension, is generally associated with greater satiety, but also diminished intestinal satiety signaling to the brain. Thus, gastric emptying may be delayed and the secretion of CCK reduced and hence satiety blunted. This, in turn may contribute to the development of obesity [62].

Further evidence for the importance of gastric capacity is the notion that dieting reduces capacity [63] and surgical reduction of the stomach reduces meal-size and induces weight loss [64]. Delayed gastric emptying due to gastric distension is generally associated with greater satiety, but also diminishes intestinal satiety signaling to the brain, such as intestinal release of CCK [65] which satiating effect might be reduced leading to obesity.

As mentioned previously, plasma levels of both GLP-1 and PYY are attenuated in the obese after a meal [38–40]. These attenuated plasma levels of GLP-1 and PYY may result in weak GLP-1 and PYY cues in the obese, which may promote an earlier onset of the next meal and thus contribute to the development of obesity. In favor for this supposition, we have demonstrated that treatment with prandial subcutaneous injections of GLP-1 over a five-day period in obese subjects resulted in decreased gastric emptying along with a modest weight loss [66].

PYY(3-36) may mediate satiety sensations by acting directly on Y2 receptors in the arcuate nucleus of the hypothalamus [55]. The effect of PYY(3-36) on gastrointestinal motility is largely unknown and it would be of interest to see whether PYY(3-36) affects the gastric emptying profile in lean as well as in obese subjects as a possible peripheral mechanism of action.

### 3.1. Central nervous system

The arcuate nucleus in the hypothalamus seems to be dominant for the inflow of peripheral signals mediating information on metabolic storage and needs, while the nucleus tractus solitarius in the brain stem is the main entry port for signals from the GI tract (Fig. 1).

There are two different populations of cells in the arcuate nucleus, which control food intake in opposite ways. One of these cell populations contains NPY, which is the most powerful stimulator of feeding behavior known so far [67]. The other cell population contains pro-opiomelanocortin (POMC) which is split into α-melanocyte stimulating hormone (α-MSH) that inhibits eating by acting on melanocortin receptors [68]. There is an inhibitory cross-talk between the two neuropeptide systems, with NPY neurons promoting not only hunger sensations, but also inhibiting satiety feelings by inhibition of the feeding-suppressive α-MSH system [69,70]. Peptide hormone receptors are located on both these two cell populations, which are regulated by leptin and insulin, which inhibit NPY-containing neurons and stimulate POMC-containing neurons. Interestingly, PYY(3-36) is considered the natural ligand for presynaptic Y2 receptors, thus inhibiting NPY release in the brain [54].

In the lateral hypothalamus, brain cells targeted by NPY- and POMC-immunoreactive neurons regularly contain the two orexigenic peptides, orexin A (OX A) and orexin B [71]. In contrast, GLP-1 is found in the solitary tract and in the dorsal and ventral medullary reticular nucleus, which corresponds to brain stem regions that collect vagal input from the gut [72]. GLP-1-immunoreactive nerve fibers are also found in the paraventricular nucleus of the hypothalamus, projecting further to hunger centers in the lateral hypothalamus and periventricular areas [72–74].
3.2. Enteric nervous system

Many of the peptides found in enteroendocrine cells of the mucosa of the GI tract and in central centers regulating food intake are also found in the enteric nervous system (ENS) and vagal afferent nerve fibers. An example of this is that neurons in the GI submucosal and myenteric plexuses, and endocrine cells in the intestinal mucosa and pancreatic islets display OXA as well as orexin receptor immunoreactivity [75,76] (Fig. 3). OXA inhibits GI motility and modulates both insulin and glucagon release in the rat [77,78].

Plasma concentrations of OXA are increased during fasting [79], and orexin-positive neurons in the gut, like those in the hypothalamus, are activated by fasting, indicating a functional response not only in the brain, but also in the GI tract [75]. It is possible, that vagal or sympathetic afferent fibers may be activated in the ENS relaying information to the CNS regarding peripheral metabolic tone. In line with this, orexin receptors are found on vagal afferent neurons in both rat and man, and may be of importance for an OXA-dependent inhibition of vagal satiety responses to CCK [80]. Intravenous administration of OXA to man does not influence appetite ratings, however plasma concentrations of leptin decrease during a 180-min infusion of OXA in man suggesting a gut-fat mass cross-talk which may be combined with other physiological signals since its CCK1 receptor is of major importance for satiety sensations. However, just to indicate how complex these mechanisms are a recent publication indicated that the combination of GLP-1 and CCK did not result in an increased satiety response in human subjects [83]. After food intake a whole array of peptides are released and the most effective combination needs to be elucidated in future studies. Recent studies of e.g., ghrelin have increased our understanding of the endocrine control of hunger and it is hoped that future research on the interactions between GI peptides and the ENS and the CNS in the control of eating behavior will increase our understanding of the development of obesity as well. Future research needs to focus on interactions between GI peptides, the ENS and CNS in the control of eating behavior and development of obesity.

4. Discussion

Our review emphasizes the peripheral signaling systems of the GI tract that underlie the intestinal control of ingestion and development of obesity. As it seems today the short-term control of ingestion is primarily controlled by signaling pathways emanating from the GI tract, being relayed through the nucleus tractus solitarius in the brain stem with further branching to higher centers of the CNS. This implies regulatory brain centers of hunger and satiety in the hypothalamus such as the arcuate nucleus, as well as other higher brain centers of reward, such as the ventral tegmental area. The long-term control of ingestion, however, is more complicated as it seems that the primary signaling emanates from peripheral tissues, mainly adipose tissue, which is to be considered as an endocrine organ releasing leptin and among others, adiponectin and resistin, to the bloodstream in order to achieve a balanced basal metabolic performance.

The initial discovery of CCK actions in the 70s, as well as later findings with GLP-1 and PYY(3-36) during the last decade is an important step in our understanding of endocrine control of satiety. Research with GLP-1 and PYY today suggests the importance of gastric and intestinal signaling to the brain in the regulation of hunger, satiety and eating behavior. Treatment with GLP-1 in over-weight subjects reduced their appetite and daily intake leading to weight control [43,44,66]. Furthermore, infusion of PYY(3-36) decreased appetite and reduced daily food intake [54] in normal, as well as obese subjects [55]. This is in contrast to other satiety-stimulating peptide hormones such as CCK, where the latency period to the next meal was shortened and therefore the daily intake was unchanged. In spite of this, CCK may be beneficial in a therapeutic setting if combined with other physiological signals since its CCK1 receptor is of major importance for satiety sensations. However, just to indicate how complex these mechanisms are a recent publication indicated that the combination of GLP-1 and CCK did not result in an increased satiety response in human subjects [83]. After food intake a whole array of peptides are released and the most effective combination needs to be elucidated in future studies. Recent studies of e.g., ghrelin have increased our understanding of the endocrine control of hunger and it is hoped that future research on the interactions between GI peptides and the ENS and the CNS in the control of eating behavior will increase our understanding of the development of obesity as well. Future research needs to focus on interactions between GI peptides, the ENS and CNS in the control of eating behavior and development of obesity.

5. Concluding remarks

Regulation of food intake seems to involve dual mechanisms. The short-term control of hunger and satiety ultimately leading to meal taking is primarily governed by gut-derived signaling to the brain, and of which ghrelin is stimulatory, whereas GLP-1 and PYY are inhibitory. The long-term control is of metabolic origin where the endocrine action of adipose tissue comes into focus, with peptide hormones such as leptin, are released in the periphery to act on centers in the brain regulating appetite and metabolic control.

Acknowledgements

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