Gastrointestinal hormones and satiety

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ABSTRACT

Individuals and animals vary the amount of food ingested on a daily basis yet manage to achieve stable body weight over extended periods of time. This control of energy balance is performed by the coordination of two important groups of signals. The first are body weight regulatory signals derived from the periphery and act as homeostatic indicators of both long-term and short-term energy stores. The second are signals synthesized and secreted primarily within the hypothalamic and brainstem regions of the central nervous system. It is through integration of all of these signals that the precise regulation of energy balance is achieved. This brief review will focus primarily upon the peripheral short-term or meal-related signals from the gastrointestinal system that are vital for proper regulation of meal size and satiety.

INTRODUCTION

The availability of energy stores within an individual is directly proportional to the amount of circulating metabolic and endocrine signals. These long-term indices of fuel availability are commonly termed "adiposity signals" such as the adipose-derived hormone leptin and circulating insulin (1). These signals act in concert with short-term meal related signals derived primarily from the gastrointestinal system to relay energy status feedback to the feeding related centers of the brain (Figure 1). If energy stores are low during periods of starvation or caloric restriction the hypothalamus orchestrates and initiates a cascade of orexigenic or hunger related signals in efforts to achieve a normal or positive energy state. Meals are initiated primarily though hypothalamic output however it is the gastrointestinal system that is responsible for the termination of eating or feelings of satiation. Hormone secretions from the gastrointestinal system act either through humoral or neural (vagal) communication to adjust meal consumption. While there are dozens of hormones secreted from specific enteroendocrine cells lining the gastrointestinal system (2, 3) this review will focus on a few of the most widely studied as well as the hormones with the most promise of therapeutic potential in the treatment of obesity and associated co-morbid conditions.

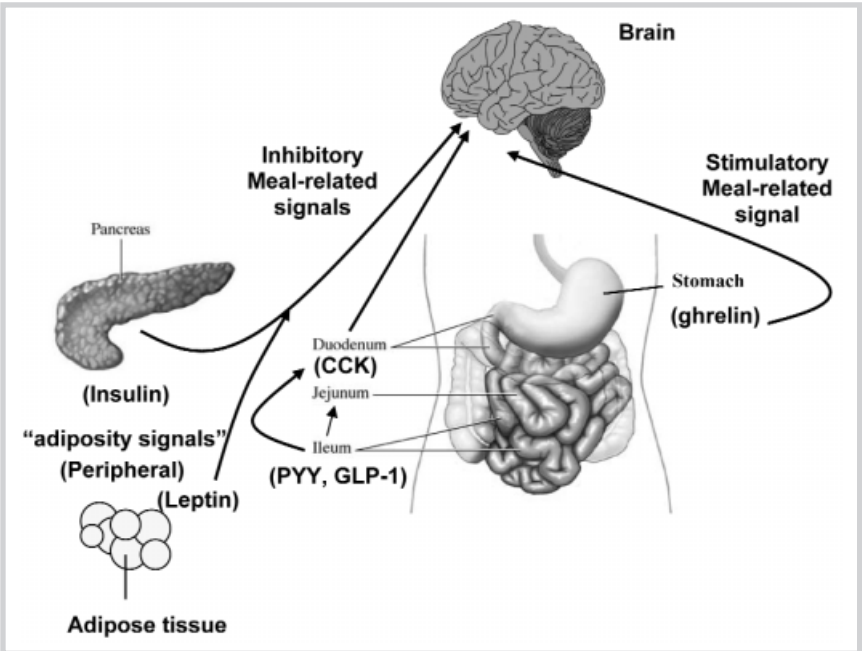

Figure 1.

CHOLECYSTOKININ (CCK)

Cholecystokinin (CCK) is the most extensively studied gastrointestinal satiety hormone and is secreted in two forms, CCK-33 and CCK-8, from the I-cells within the proximal intestinal tract, the duodenum and jejunum (4). CCK is secreted primarily by the ingestion of fat and protein in chyme that comes into contact with the CCK secreting "I" cells that line the intestinal tract (5, 6). Following stimulation of these cells CCK is released and mediates its' effects through interactions with two receptors CCK-1 and CCK-2, previously named CCK-A (for alimentary) and CCK-B (for brain). The physiological effects of secreted CCK on the gastrointestinal system (for review see7) include the regulation of gastric secretions and emptying, intestinal motility, gall bladder contractions, and pancreatic enzyme secretions (8, 9).

The first experiments examining the role of exogenous CCK on food intake were performed more than 30 years ago by Gibbs and Smith. In these experiments both purified and CCK-8 were administered intra-peritoneally into rats significantly reduced meal size (10). Subsequently, it was determined that CCK delivered directly into the central nervous system will also reduce meal size (11, 12). Since these initial reports many laboratories have replicated and extended these findings in both non-human primates and humans (13, 20). In support of CCK as an important regulator of meal size is the finding that antagonism of endogenous CCK-1 receptors will result in an increase in meal size in both experimental animals and humans (21, 24). Additionally, rats with spontaneous

mutations of the CCK-1 receptor (called OLETF rats) eventually become obese during their lifespan (25, 26).

Despite the unequivocal evidence that endogenous CCK is an important satiety factor, its' potential as a long-term inhibitor of hunger may be limited. This was determined in a series of studies by West *et al* who demonstrated that acute injections of CCK will reduce meal size however repeated or long-term injections of CCK have no effect on weight loss (27, 28). Initially, rats will reduce meal size but they soon learn to compensate by increasing the frequency of daily meals. Together these studies determined that CCK is truly a short acting regulator of meal size.

Because human eating disorders are characterized by either reduced meal size (anorexia) or increased meal size or lack of satiety (bulimia), CCK makes a likely candidate for investigation. In fact, for both bulimia (29, 31) and anorexia (32) perturbations in the secretion of CCK have been documented. Because of these associations the development of long acting CCK antagonists or agonists may prove beneficial in the treatment of these abnormalities of eating behavior.

GLUCAGON LIKE PEPTIDE (GLP-1) AND PEPTIDE YY (PYY)

Located within the ileum of the small intestine and colon are enteroendocrine "L" cells that synthesize and secrete both glucagon like peptide-1 (GLP-1) and peptide YY (PYY) (33, 34). Both of these hormones are synthesized and derived from larger precursor molecules (33, 34) and are secreted from essentially the same cells within the ileal and colonic mucosa immediately following ingestion of a meal. The endogenous stimulation of these hormones is nutrient dependent with carbohydrates and fats as the most effective stimulators (34, 35). Because the site of synthesis and secretion for both of these hormones is extremely distal in the intestinal tract it has become clear that both nutrient and neurohumoral stimulation is required for their release.

The importance of both GLP-1 and PYY in the regulation of satiety has been established in many ways. In both rodent and human studies it has been shown that exogenous peripheral and central administration of GLP-1 and PYY will reduce food intake (36-45). Although the evidence is quite convincing that GLP-1 is an important satiety factor, there remains controversy with regards to the anorectic effects of PYY (46-52). Much of the controversy stems from the various forms of circulating PYY. Peptide YY circulates as both PYY (1-36) and PYY (3-36). These two forms have varying affinities for the receptors that mediate the anorectic effects of PYY. Among the many receptors that are capable of binding members of the PYY family, the Y2 receptor appears to be the receptor responsible for the anorectic effects. PYY (3-36) reduces food intake by interacting with this receptor.

In support of this is the evidence that PYY (3-36) is ineffective in reducing food intake in the Y2 deficient mouse (53).

Reductions in food intake by both GLP-1 and PYY may be mediated by gaining access and acting directly on feeding centers within the central nervous system (37, 41-45, 54-58) or by interacting with receptors on vagal afferents. Another important physiological effect of both GLP-1 and PYY is the ability to reduce gastric emptying and inhibit gastrointestinal motility (54, 59, 60).

In the specific case of GLP-1 there appears to be clear potential for the development of effective treatments for obesity. One obstacle that is limiting the development of such treatments is the rapid degradation of endogenous and exogenous GLP-1. GLP-1 is degraded within 90 seconds by the enzyme DPP-IV. In efforts to overcome this limitation the use of long-acting GLP-1 receptor agonists have been utilized. Exending-4, a
39-amino acid peptide originally isolated from the salivary gland of the reptile the Gila monster is a potent and long-acting agonist for the GLP-1 receptor (half-life longer than 30 minutes) (61, 62). In humans and animals exendin-4 has been demonstrated to reduce gastric emptying, lower plasma glucose and reduce food intake (63-65). The development of agonists for the GLP-1 receptor appears to be very promising for both treatments of obesity and associated diabetic conditions.

GHRELIN

Ghrelin is one of the most recently discovered gastrointestinal hormones and it is unique in that it appears to be clearly an orexigenic signal rather than an anorectic signal like the vast majority of the other described gastrointestinal hormones. Ghrelin is synthesized and secreted primarily from the fundic mucosa of the stomach and increases in states of hunger or food deprivation (66). In addition exogenous ghrelin administration both peripherally and centrally increase food intake in rodents (67-69). Unlike the previously described hormones, ghrelin does not appear to signal satiety but rather increases in the plasma in anticipation of a meal and falls immediately after the consumption of food (66). In contrast to adiposity signals like leptin and insulin, plasma ghrelin concentrations increase in direct proportion to lean body mass. One study in particular that was a catalyst for further studies in regards to the relevance of ghrelin as an endogenous regulator of feeding behavior addressed the effects of gastric bypass surgery on circulating ghrelin (70). In this study Cummings *et al* demonstrated that patients with gastric bypass surgery demonstrated a near abolishment of plasma ghrelin. This study suggested that the reduction in hunger and food intake following surgical procedures such as gastric bypass maybe in part mediated by the reduction in plasma ghrelin.

SUMMARY

Within the last 40 years there has been a dramatic increase in the discovery of gastrointestinal hormones that are important in energy balance regulation (2). In combination with the advanced knowledge of the mechanisms underlying these hormones and the development of specific murine knockout models for many of the identified hormones it is likely that better therapeutic treatments for obesity and eating disorders will be generated. Additionally, surgical treatments for obesity such as gastric bypass have provided unparalleled treatments for morbid obesity resulting in long lasting weight loss and minimal recidivism. These surgical procedures have recently demonstrated increases in many of the anorectic hormones described above such as CCK, GLP-1 and PYY as many as 20 years after surgery (71) and reductions in ghrelin as mentioned above (70, 71). Because surgically-induced weight loss is so effective further studies are warranted to fully understand their underlying mechanisms.

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