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APPETITE REGULATION BY GUT PEPTIDES

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CONTENTS

It is generally accepted that food ingestion is regulated by a central feeding drive that is held in check by a peripheral satiety system during meal feedings (41). The major component of the peripheral satiety system responsible for terminating a meal appears to be the release of gastrointestinal peptides in response to the passage of food through the gut. The central feeding drive system includes a number of anatomical sites such as the paraventricular and

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ventromedial nuclei of the hypothalamus and structures associated with the fourth ventricle. Within these sites the interaction of a number of neurotransmitters including norepinephrine, dynorphin, and neuropeptide Y is believed to be responsible for the generation of the feeding drive (42). In addition to the short-term peripheral satiety system responsible for the termination of a meal, a longer-term peripheral satiety system includes the effects of absorbed nutrients and of hormones released from the ileum. A combination of all these factors is responsible for the regulation of food intake in a given individual.

PHYSIOLOGICAL EVIDENCE FOR THE PRESENCE OF CIRCULATING SATIETY FACTORS

In 1912 Carlson (8) and Cannon & Washburn (7) suggested that gastric distension was responsible for the initiation of satiety. Animals with fistulas that prevent food from entering the stomach eat continuously. In 1949, Janowitz & Grossman (28) found that distension of a balloon in the stomach of a dog resulted in satiety. Infusion of 4 to 8 cc of a liquid diet into a transplanted extra stomach in a rat results in reduced food intake, thus demonstrating that signals from a totally denervated stomach can alter food intake (30). These results show that humoral factors play a role in producing stomach satiety. In rhesus monkeys, the stomach can monitor caloric content of food and regulate food intake based on its caloric content (38). In humans pentoses have less caloric content than hexoses but are much greater inhibitors of gastric emptying (57). Xylitol preload not only markedly suppressed gastric emptying but also decreased food intake in humans (58). Inhibition of food intake by the stomach occurs when the stomach is distended at least 20% in excess of normal size during food intake.

In parabiosis experiments, when the duodenum of one rat is connected to the stomach of another rat, feeding the second rat leads to a decrease in food eaten by the rat whose duodenum is exposed to the food, which suggests that food in the intestine results in satiety (32). Distention of the duodenum by infusion of nonnutritive foods leads to decreased food intake (12), and a further decrease in food intake was produced by the addition of nutrients to the perfusate (16). Cross-perfusion of rats has shown that the unfed rat will eat much less than normal when cross-perfused with the blood of a fed rat (13). Parabiosis of normal rats to rats with ventromedial hypothalamic lesions resulted in decreased food ingestion by the normal rat and may be due to overproduction of circulating satiety factors.

These studies support the concept that the release of hormones from the stomach and intestine helps modulate food intake.

CHOLECYSTOKININ: THE PROTOTYPIC PERIPHERAL SATIETY HORMONE

Cholecystokinin (CCK), a 33-amino-acid hormone, was first isolated from the gastrointestinal tract by Mutt & Jorpes in 1971 (49). CCK has multiple effects on the gastrointestinal tract and the central nervous system. The history of CCK as a satiety hormone predates its isolation. In 1937 MacLagan (36) showed that crude duodenal extract, which contains CCK, decreases food intake. Similar findings were reported by Ugolev & Kassil (69) in 1961 and Schally et al (55) in 1967. The first attempt to demonstrate that a highly purified CCK preparation decreased appetite was by Glick et al (25) in 1971. Although they concluded that CCK-pancreozymin did not statistically suppress food intake in rats, their results demonstrated a clear trend towards suppression of food intake. The following year, Sjodin (63) reported that CCK decreased food intake in dogs. In 1973, Gibbs et al (24) reported that the biologically active form of CCK, the sulfated octapeptide, reduced food intake in rats.

CCK has been shown to decrease food intake in multiple species (see 45 for a review). CCK appears to be more potent when administered peripherally that when injected into the cerebral ventricles in most but not all species tested. These findings suggest that the major site of action for the satiety effect of CCK is peripheral, rather than central. In addition, intraperitoneal injections produce greater satiety than subcutaneous, intravenous, or intraportal injections. Thus the satiety response elicited by CCK is likely related to the effect of CCK on the gastrointestinal tract or on a closely related structure, the vagus.

Transection of the vagus nerve trunk inhibits the satiety effect of CCK at low (65), but not high, doses (19). Selective gastric, but not coeliac, vagotomy also removes the ability of CCK to inhibit food intake (65). Lesioning of the afferent vagal nerve fascicles where they enter the spinal cord also attenuates the effect of CCK on food intake (66). The vagus nerve contains CCK receptors (75), and thus CCK may activate the vagus directly in a paracrine manner. Alternatively, CCK receptors also exist in the pylorus of the stomach, and CCK may activate ascending vagal fibers indirectly and secondary to its effects on the pryolic musculature. Capsaicin, which damages vagal afferents, inhibits the ability of CCK to decrease food intake (53).

Direct connections between the peripheral vagus nerve and the central nervous system have been demonstrated by electrical stimulation studies. Dyball & Koizumi (15) found that paraventricular unit activity can be modulated by electrical stimulation of the central stump of the vagus. In addition, peripheral administration of CCK-8S activates ascending vagal fibers and induces electrical activity in the nucleus tractus solitarius (17). The terminal

fields of gastric vagal afferent neurons project onto the nucleus tractus solitarius in the medulla, and lesions of this area inhibit the satiety effect of peripherally administered CCK (70).

Whether the satiety effect of CCK occurs within the nucleus tractus solitarius itself or whether the latter is merely a relay station sending messages to other central nervous system structures is unclear at the present time. Neuroanatomical studies have demonstrated direct projections from the nucleus tractus solitarius to the paraventricular, dorsomedial, and arcuate nuclei of the hypothalamus (52). Some studies have demonstrated that lesioning these pathways or the paraventricular nucleus of the hypothalamus will attenuate the effects of CCK on food intake (10, 11). On the other hand, despite using two different kinds of knife cuts, we were unable to duplicate the knife-cut studies (J. Steinman, M. Gunion, and J. E. Morley, unpublished observations).

Whether or not CCK produces true satiety and whether it is merely an aversive, rather than a toxic, agent is a matter of controversy. Much of the evidence that CCK produces aversion has come from studies using the conditioned taste aversion model. Although the results are somewhat controversial, CCK appears to be capable of producing a conditioned taste aversion (14). Unfortunately, so do a variety of other nonaversive substances including intraduodenal sesame oil and glucose, amphetamines, lorazepam, and even intravenous saline (see 5 for a review). This conditioned taste aversion can be used as a model for novelty learning, but it cannot be used to determine the aversive nature of other compounds. In the differential satiety model for aversion developed by Billington et al (5), they argue that as you increase the strength of the feeding drive (longer periods of starvation), true satiety agents become less effective at any given dose and aversive agents become equally disruptive regardless of the period of starvation. In their model, lithium chloride behaves as an aversive agent while CCK behaves as a true satiety agent. Recently, using a lever press apparatus and milk as a reward in a study of mice, we found a similar relationship between CCK and the state of hunger that confirmed that CCK is a true satiety agent (J. F. Flood and J. E. Morley, unpublished observations).

The effects of CCK in dietary selection studies are controversial. CCK has been shown to preferentially reduce either carbohydrate or fat, depending on the experimental paradigm (54). It seems that CCK may reduce food intake across the board and not demonstrate selectivity of any specific macronutrient. In addition, while CCK has been claimed to decrease food but not water intake, this selectivity appears to be both species and strain specific and has shown that CCK reduces water intake in a number of rodent strains.

The evidence that CCK is a physiological satiety agent is mounting.

1. CCK decreases food intake without producing aversion (differential satiety model).
2. Doses of CCK that reduce food intake are within the range expected for a paracrine effect.
3. The lowest doses of intraperitoneal CCK that reduce feeding produce CCK levels of the same magnitude as those seen after feeding.
4. L-phenylalamine, but not D-phenylalamine, decreases food intake and releases CCK.
5. Trypsin inhibitors release CCK and decrease feeding.
6. CCK antagonists increase food intake under certain conditions.

Although the dose of CCK required to inhibit feeding is five times higher than the dose required to stimulate pancreatic amylase secretion, one should not necessarily conclude that the effect of CCK on feeding is nonphysiological. In the case of food intake, CCK acted both as a paracrine and as a hormone to produce its effect on pancreatic secretion and gallbladder contraction. This concept is supported by the finding that the lowest doses of intraperitoneal CCK that decrease feeding produce circulating CCK levels of the same magnitude observed after feeding (64). L-phenylalanine and the trypsin inhibitor trasylol both release CCK and decrease food intake (23, 39). Use of the somewhat impure CCK antagonists proglumide and benzotript yielded inconsistent findings and the suggestion that food intake may increase when these antagonists are administered separately (60).

Recently, L-364,718, a highly selective and potent peptide antagonist of peripheral CCK receptors, has become available. In our studies L-364,718 reversed the ability of CCK-octapeptide to decrease food intake (62). It enhanced food consumption in both nonfasted and prefed mice. The number of reinforcements (a lever press was used) was also enhanced by L-364,718 compared with the results obtained with control mice. However, this agent did not enhance food intake in all paradigms. Together with other studies (1, 26), these results are compatible with the suggestion that cholecystokinin plays a physiological role in the regulation of food intake.

While the predominant effect of CCK on food intake is observed following peripheral injection, it should be remembered that CCK also affects food intake after central injection [in sheep the brain appears to be its predominant site of action (see 45 for a review)].

Intravenous CCK infusions have been shown to decrease food intake in lean and obese humans by 12 to 16% in a dosage of approximately 60 to 100 ng/kg (see 2 for a review). These doses do not appear to produce significant nausea. CCK-8S has failed to decrease feeding in vagotomized humans (59) or in a human with a lesion of the ventromedial hypothalamus (34). These

findings suggest that the pathways involved in CCK-induced satiety in humans may be similar to those observed in rodents.

The role of CCK in the binges associated with bulimia has been studied. Mitchell et al (40) reported that CCK-8 failed to limit the size of the binge. In the same set of studies the opioid antagonist naloxone did attenuate the size of the binge. This finding suggests that bulimic patients may be specifically nonresponsive to the satiety effect of CCK. In addition, CCK levels are suppressed in bulimic patients (21). These CCK levels returned to normal following antidepressant therapy. Thus abnormalities in the regulation of CCK may be involved in the pathogenesis of bulimia.

It is now well recognized that anorexia may develop with advancing age (48). In rodents, Silver et al (61) have found that the satiety effect of CCK is enhanced with advancing age. This observation is in keeping with the early satiety often present in older individuals. CCK may be involved in the pathophysiology of the anorexia of aging.

In summary, there is mounting evidence that the release of CCK from the gut is involved in the physiological termination of a meal. Preliminary studies suggest a role for CCK in the pathophysiology of bulimia and the anorexia of aging; further studies are needed to confirm these hypotheses.

CHOLECYSTOKININ, FEEDING, AND MEMORY

Feeding has long been recognized as a potent reward to reinforce learning. Until recently, however, the mechanism by which feeding enhanced memory retention had not been studied. Scientists now understand that food in the gut releases CCK, which transmits messages to the central nervous system via the afferent vagal fibers, and they hope to determine whether or not release of CCK plays a role in the enhanced memory retention associated with feeding. The hypothesis that CCK enhances memory retention is supported by the finding that direct anatomical projections connect the nucleus tractus solitarius to the amygdala (52) and that stimulation of the vagus alters activity of units in the central nucleus of the amygdala (51).

The demonstration that CCK injected intraperitoneally in the mouse enhanced memory retention and that this effect was blocked by vagotomy (19) provided further support for this hypothesis. Subsequent studies have shown that the enhanced memory retention seen in an aversive training paradigm following food administration can be inhibited by the specific CCK antagonist L-364,718 (18). We have previously suggested that a link may have evolved between the release of gastric peptides and memory processing in the central nervous system because of the survival advantages that accrue to an animal who can remember the details of a successful food-foraging expedition (19).

Table 1 Gastrointestinal and pancreatic hormones that modulate food intake after peripheral administration[a]

Hormone	Effect on food intake	Dependence on vagal nerve
Cholecystokinin	Decrease	Yes
Bombesin	Decrease	Partially
Gastrin-releasing peptide	Decrease	?
Somatostatin	Decrease or no effect	Yes
Litorin	Decrease	?
Motilin	Increase	?
Thyrotropin-releasing hormone	Decrease	Yes
Insulin	Increase	No
Glucagon	Decrease	Yes
Satietin	Decrease	?

[a] ? = not studied.

OTHER GUT HORMONES AND FEEDING

In addition to CCK, a number of other gastrointestinal hormones that are released during the passage of food through the gastrointestinal tract have been shown to modulate food intake (Table 1). Like CCK, many of these hormones also modulate food intake after injection into the central nervous system.

Bombesin, a tetradecapeptide originally isolated from frog skin, and its mammalian counterpart, gastrin releasing peptide (GRP), decrease food intake in rodents (42). Bombesin is less potent (on a molar basis) than CCK at reducing food intake (22). Subdiaphragmatic vagotomy fails to suppress the effect of bombesin on food intake (46). A combination of vagotomy and spinal visceral disconnection was shown to decrease the effect of bombesin on food intake (68). Bombesin decreased food intake in humans at doses below the threshold for nausea (50).

Somatostatin is a cyclic tetradecapeptide that reduces feeding in baboons and rats (35). Somatostatin is effective only in animals with very mild degrees of hunger (33). Vagotomy abolishes the effects of somatostatin on food intake (33). Feeding hydrolyzed gluten to humans results in a physiological increase in somatostatin (47). This physiological increase in somatostatin did not alter either food intake or appetite as measured on an analog scale.

Thyrotropin-releasing hormone (TRH) is present in the gastrointestinal tract and pancreas as well as in the brain (44). TRH decreases food intake after peripheral administration, and its effects appear to be vagally dependent (46).

Motilin is a 22-amino-acid peptide whose levels increase with feeding. Motilin administration enhances food intake, possibly secondary to its ability to increase the number of stomach contractions that promote gastric emptying and minimize gastric distension (9).

PANCREATIC HORMONES

In 1924 the ability of insulin to stimulate feeding in humans was demonstrated (3). The major sensor for the acute effect of insulin on feeding is the liver, and the effect of insulin on feeding can be blocked by vagotomy (42). Insulin can also enhance feeding by producing central glucoprivation.

A conundrum is that centrally administered insulin and very low doses of insulin administered by constant infusion peripherally inhibit feeding (71, 73). Insulin antibodies administered into the ventromedial hypothalamus will enhance feeding (67). Thus insulin like a number of other peptides, e.g. neuropeptide Y and beta-endorphin, appears to have opposite effects when administered peripherally or centrally. These findings have led to the development of the yin-yang theory of energy regulation. According to this theory, substances that mobilize energy resources peripherally will enhance feeding when administered centrally, and agents that promote energy storage will decrease feeding when administered centrally. The teleological advantage of a close linkage between the regulation of energy reserves and the activation of food-seeking behaviors in an organism is obvious.

In 1957 Schulman et al (56) demonstrated that glucagon decreased food intake in humans. The major site of action for glucagon's suppressive effects on feeding appears to be the liver. Glucagon antibodies enhance meal size and duration; therefore the effect of glucagon on feeding is most probably physiological (31). The satiety effect of glucagon is impaired by selective hepatic vagotomy (20).

To summarize, both glucagon and insulin appear to be physiological regulators of feeding and energy metabolism.

THE ILEUM AND SATIETY

Intestinal bypass surgery in humans is associated not only with weight loss secondary to malabsorption but also with a decrease in food intake (6). Jejunoileal bypass in obese rats has also been shown to reduce food intake (37). Atkinson & Brent (2) have noted that a factor with appetite suppressant activity appears in the serum of rats that have undergone intestinal bypass surgery. At present this factor is poorly characterized.

SATIETINS

Using human and rat blood, Knoll (29) partially purified long-acting anorectic glycoproteins with a molecular weight of 50,000. He named these substances satietin and satietin D. Although the onset of action by satietins is slow, the duration of action can extend to 48 h. Satietins produce their effects after both peripheral and central administration. These satietins possibly may play a role in the modulation of long-term food intake, and hyposatietinemia may affect some forms of obesity. The full characterization of the structures of the satietins will be necessary before the physiological role of these glycoproteins in the regulation of food intake can be determined.

INTERACTIONS

Peripheral Interactions

Hinton et al (27) reported that the combined administration of pancreatic glucagon, CCK-8, and bombesin produced a greater reduction in feeding than when any of these hormones were given alone. We have found that CCK-8, glucagon, and somatostatin (when administered in combination) have an additive effect on reducing food intake (A. J. Silver, J. F. Flood, and J. E. Morley, unpublished observations). On the other hand, the combination of CCK-8 and bombesin was invariably infra-additive, and somatostatin inhibited the effects of bombesin. Bombesin down-regulates CCK receptors (74), thus providing a possible explanation for the infra-additivity of CCK and bombesin. One can safely conclude that gastrointestinal hormones released from various levels of the gut during feeding act together in an additive manner that results in the termination of a meal.

Central and Peripheral System Interactions

In a series of pharmacological studies we have demonstrated that peripheral hormones can attenuate the feeding produced by centrally active neurotransmitters such as norepinephrine and dynorphin (see 42 for a review). Previously, we hypothesized that primitive organisms possess only a feeding drive. The evolution of an energy storage system allows the organism to develop a peripheral satiety system so that it can become a meal feeder. This hypothesis is supported by current studies demonstrating that peripheral gastrointestinal hormones can attenuate the central feeding drive.

GUT PEPTIDES AND ENERGY METABOLISM

While it is clear that gut peptides can limit the size of a single meal, there is little evidence that prolonged administration of gut peptides will cause weight

loss. Tolerance to the anorectic effects of CCK and bombesin develops rapidly after peripheral administration (4). This tolerance appears to be behavioral, rather than pharmacological, as CCK continues to decrease meal size, but the animals reduce the inter-meal interval to maintain food intake (72). Glucagon reduces food intake after a single meal, but when chronically administered it produces weight loss while actually increasing food intake (4). The weight loss produced by chronic glucagon administration appears to be secondary to activation of brown adipose tissue. A gut peptide that has no effect on food intake when administered peripherally is Peptide YY, a member of the pancreatic polypeptide family. Chronic administration of Peptide YY leads to weight loss (43). Peptide YY is present in the blood vessels associated with brown adipose tissue, and it may induce weight loss by acting synergistically with norepinephrine to activate brown adipose tissue.

It seems clear that gastrointestinal peptides not only play a role in the regulation of food intake but also modulate energy metabolism.

SUMMARY

A number of gastrointestinal hormones that are released from the gut in response to intraluminal food stuffs have been shown to play a role in producing satiety. Some of these hormones apparently activate ascending vagal fibers that send messages to the nucleus tractus solitarius, and perhaps from there messages are sent to the paraventricular nucleus of the hypothalamus. Not only do gastrointestinal hormones play a role in the termination of a meal but they also appear to modulate energy metabolism (at least in rodents) through the activation of brown adipose tissue.

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