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Gastrointestinal Satiety Signals
I. An overview of gastrointestinal signals that influence food intake

Stephen C. Woods
Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio 45267

Woods, Stephen C. Gastrointestinal Satiety Signals. I. An overview of gastrointestinal signals that influence food intake. *Am J Physiol Gastrointest Liver Physiol* 286: G7–G13, 2004; 10.1152/ajpgi.00448.2003.—An overview is presented of those signals generated by the gastrointestinal (GI) tract during meals that interact with the central nervous system to create a sensation of fullness and satiety. Although dozens of enzymes, hormones, and other factors are secreted by the GI tract in response to food in the lumen, only a handful are able to influence food intake directly. Most of these cause meals to terminate and hence are called satiety signals, with CCK being the most investigated. Only one GI signal, ghrelin, that increases meal size has been identified. The administration of exogenous CCK or other satiety signals causes smaller meals to be consumed, whereas blocking the action of endogenous CCK or other satiety signals causes larger meals to be consumed. Satiety signals are relayed to the hindbrain, either indirectly via nerves such as the vagus from the GI tract or else directly via the blood. Most factors that influence how much food is eaten during individual meals act by changing the sensitivity to satiety signals. This includes adiposity signals as well as habits and learning, the social situation, and stressors.

cholecystokinin; adiposity signals; ghrelin; bombesin

THE GASTROINTESTINAL (GI) tract accepts ingested food and processes it mechanically and chemically to render what has been eaten into small, absorbable units. Hence, carbohydrates are processed in the stomach and intestine to monosaccharides such as glucose and fructose, most lipids are digested to fatty acids and monoacylglycerols, and proteins are digested to amino acids. These monosaccharides, fatty acids, and monoacylglycerols (resynthesized to form triacylglycerols in the intestinal epithelial cells), amino acids, plus micronutrients, such as vitamins and minerals, are subsequently absorbed into the body. The overall process of digestion is coordinated by interactions of the enteric nervous system, which innervates the walls of the GI tract, plus numerous hormonal and other chemical signals generated by cells embedded in the wall of the gastrointestinal tract. The object of this theme article is to review the role of some of these chemical signals in influencing food intake. As a group, these are called satiety signals, because most of them create a sensation of fullness in humans and cause food intake to be reduced when administered to humans or animals. At least one of the GI signals, ghrelin, appears to have the opposite effect, stimulating enhanced food intake.

Satiety signals are so named because when they are administered to animals before a meal, a decrease in the size of that meal is observed. Several other criteria must be met, however, before a hormone, neurotransmitter, or other internal signal is considered a satiety signal. For one, if the signal influences the size of normal meals, it should be the case that blocking or compromising its endogenous activity leads to increased meal size. That is, the administration of an antagonist to the signal or the generation of an animal lacking a receptor for the signal should be associated with consumption of greater than normal amounts of food. Another criterion is that the reduction of food intake caused by administration of the "satiety" signal should not be the consequence of illness or malaise, or of some sort of incapacitation, and the animal (or person) receiving the compound should engage in behaviors that occur when meals end naturally. That is, there are many reasons why the administration of an exogenous compound might cause an animal to eat less food, reasons that have little or nothing to do with normal satiety. Finally, the secretion of an endogenous satiety signal must be elicited by ingested food with a temporal profile consistent with contributing to the normal cessation of eating. These criteria are well accepted (26, 70, 71, 82).

MEALS

Food intake occurs in distinct bouts or meals, with the frequency and size of individual meals over the course of a day comprising an individual's meal pattern. Most animals, including humans, have habitual meal patterns, consuming approximately the same number of meals and at the same times of day each day. Within a given species, however, there is considerable variation among individuals in terms of the number of meals as well as the spacing and size of each meal. The factors that control when meals occur are distinct from those that control when they end; i.e., different factors control meal onset and meal size. Until the last 25 years, meal onset was thought to be under the control of factors related to immediately available energy. The most popular position was the glucostatic theory, which postulated that a reduction of glucose utilization by sensor cells in the hypothalamus caused sensations of hunger and increased the likelihood of starting a meal. Food intake was hypothesized to cause a consequent increase in glucose utilization, the sensation of satiety, and cessation of eating (40, 41). Other hypotheses related to available energy have been based on body heat, fat utilization by the liver, and the generation of ATP and other energy-rich molecules by the liver and/or brain (34). For the most part, these hypotheses have not withstood the test of time, in large part because other kinds of signals were discovered to be more likely endogenous controllers of meals.

It is generally accepted today that whereas a decrease in available energy or its utilization can cause an individual to begin eating at a time it ordinarily would not, the decrease of glucose or another energy source is considerably larger than what occurs normally, and the eating in that instance is considered to be an emergency response (34). Current thinking is that most meals are initiated at times that are convenient or habitual and thus are based on social or learned factors as

Address for reprint requests and other correspondence: S. C. Woods, Dept. of Psychiatry, Box 0559, 231 Albert Sabin Way, Univ. of Cincinnati, Cincinnati, OH 45267 (E-mail: steve.woods@psychiatry.uc.edu).

opposed to adjustments of energy within the body. Because of this, the regulatory control over food intake is manifest over how much food is consumed once a meal begins rather than on when the meal will be initiated (83). This type of control allows considerable flexibility, such that individuals can adapt their meal patterns to their environment and lifestyle while still maintaining control over the amount of food consumed and integrating it with body fat. Hence, regulatory controls determine meal size, and this is generally equated with the phenomenon of satiety or fullness.

SATIETY SIGNALS AND ADIPOSITY SIGNALS

Figure 1 depicts the types of signals that influence food intake. Although it is an oversimplification, these signals can be separated into three major categories: satiety signals, adiposity signals, and central effectors. Satiety signals are those arising from the GI tract and related organs during a meal. These signals influence eating behavior by activating neurons in the nucleus of the solitary tract (NTS) in the hindbrain. Although there are minor variations in the exact pattern, most satiety signals interact with specific receptors on peripheral nerves passing from the GI tract to the hindbrain, especially the vagus nerves (e.g., CCK and glucagon), or else circulate to the hindbrain via the blood and interact with local receptors there (e.g., amylin). Adiposity signals, in contrast, are hormones secreted into the blood in direct proportion to the amount of stored body fat. The two adiposity signals that are best known are insulin and leptin. Insulin is secreted from pancreatic β-cells in response to increases of glucose. However, basal insulin in the absence of elevated glucose, as well as every increment of insulin above baseline during meals, is in direct proportion to total body fat or adiposity (3, 55). Obese individuals have relatively high basal and stimulated insulin, whereas lean individuals have relatively low levels (81). Leptin is secreted from fat cells (adipocytes) in direct proportion to the amount of stored fat (2, 12, 28, 29). Hence, circulating insulin and leptin levels are each a good indicator of body fat, and both hormones are able to enter the brain from the blood and stimulate specific receptors on neurons. Although many areas of the brain are sensitive to insulin and leptin, neurons in the

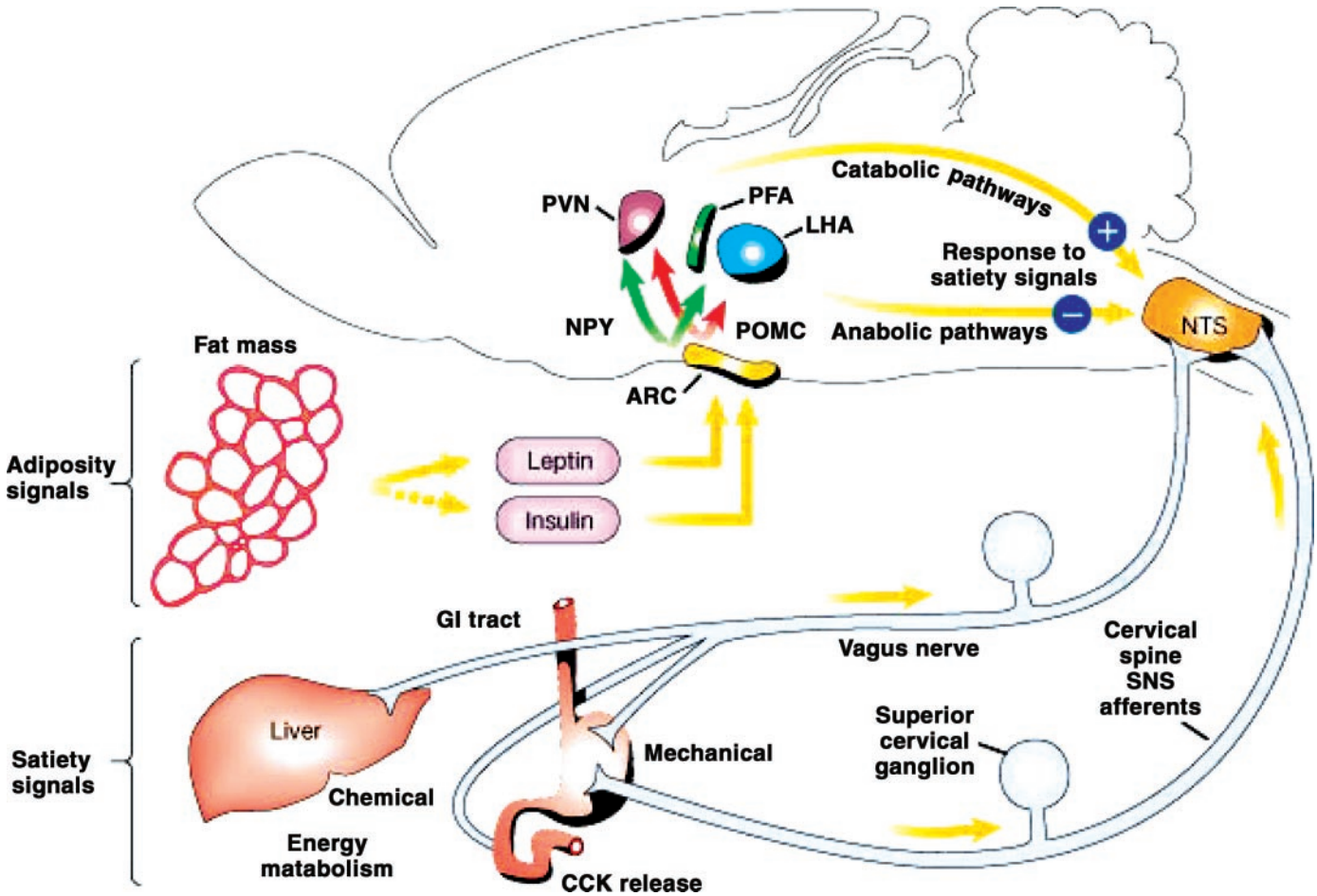

Fig. 1. Model depicting signals that influence food intake. Hormones whose secretion and circulating levels are directly proportional to body fat (leptin and insulin) are called adiposity signals and interact with the brain at the hypothalamic arcuate nucleus (ARC). Satiety signals are generated in the gastrointestinal (GI) tract during meals and provide information about mechanical (e.g., stomach stretch, volume) and chemical properties of the food (as indicated by CCK release). The signals are conveyed via sensory axons in the vagus and sympathetic (SNS) nerves into the nucleus of the solitary tract (NTS) in the brain stem. Within the brain, neural circuits integrate information from the NTS and several hypothalamic nuclei [ARC, paraventricular (PVN), lateral hypothalamic (LHA), and perifornical (PFA)] to determine food intake and energy expenditure (from Ref. 68). POMC, proopiomelanocortin.

arcuate nucleus of the hypothalamus have particularly high levels of their receptors (see Fig. 1). The ability of insulin and leptin to function as adiposity signals to the brain has been reviewed several times (1, 5, 20, 52, 68, 84).

Central effector signals arise from circuits that receive inputs from satiety signals and adiposity signals and integrate them with inputs from several other brain areas. In this way, factors such as learning and habits, the social situation, stress and emotions, and many others are able to interact with metabolic factors to influence food intake. Central effector systems are partitioned into those that create a net catabolic response and those that create a net anabolic response. A catabolic response includes reduced food intake and increased energy expenditure, and if it is prolonged over days, leads to loss of body weight as well. Anabolic responses are the opposite and include increased food intake and reduced energy expenditure and lead to increased body weight on a chronic basis. The adiposity hormones insulin and leptin elicit a net catabolic response in the brain. If insulin or leptin levels are increased locally within the brain, animals eat less food and lose weight; if the normal leptin or insulin signal within the brain is reduced, animals overeat and become obese (see Refs. 68 and 84 for reviews).

SATIETY SIGNALS

As discussed above, regulatory controls over food intake are exerted on how much food is eaten during a meal as opposed to when that meal begins. Because of this, the individual must have a means of measuring reliably how much food has been eaten at any point within a meal; i.e., the number of calories consumed or the relative amounts of carbohydrates, lipids, proteins, and/or any other food-related parameters must be monitored continuously to enable the individual to stop the meal at the appropriate point. In principle, any number of parameters could provide the key feedback during an ongoing meal. For example, the individual might use sight, smell, or taste to estimate how much energy has been consumed. However, experiments in which animals have an implanted gastric fistula have rendered such explanations unlikely. When the fistula is closed (real eating), swallowed food enters the stomach, is processed normally, and is passed into the duodenum. When the fistula is open, swallowed food enters the stomach normally but exits the body via the fistula, a process called sham eating. In both instances the visual, olfactory, and taste inputs are the same, but the amount eaten varies considerably. When the fistula is closed, animals eat normal meals; when the fistula is open (sham eating), they continue eating for long intervals and consume very large meals (18). Hence, whatever signals are used to gauge how many calories have been consumed must arise beyond the distal stomach and/or small intestine.

As food interacts with the lining of the stomach and intestine, a complex array of gut peptides and other signals that function to coordinate and optimize the digestive process are secreted. Some of these enter the lumen to interact with the food directly, others are secreted into the local interstitial fluid to influence neighboring cells in a paracrine fashion, and still others enter the blood as hormones to influence more distant target organs such as the liver, pancreas, or brain. These signals collectively ensure that the appropriate mix of enzymes and other factors are added to the ingested food in the right sequence and that the mixture is passed along the GI tract at the appropriate speed. Some of these same signals also provide information to the central nervous system and thereby function as satiety signals.

CCK

Any endogenous factor that causes a sensation of fullness and reduces the size of an ongoing meal is called a satiety signal, and several different GI peptides are thought to meet this criterion. Having a number of different satiety signals enables species that are general omnivores, such as rats and humans, that eat plants, other animals, or any other nutrient source to eat whatever food is available and to secrete a cocktail of gut peptides appropriate for digesting the particular food being eaten while at the same time informing the brain as to precisely what has been consumed. Different signals are secreted in response to specific carbohydrates, fats, proteins, or mixtures of these macronutrients, and it is the specific mix or cocktail of signals that presumably informs the brain as to what precisely has been eaten. Table 1 lists the peptides secreted from the digestive system that have been found to alter meal size. By monitoring signals that are correlated with ingested calories, the brain is able to terminate a meal when ample calories have been ingested but well before they have entered the blood in significant amounts. This ability is important for preventing the body from becoming overwhelmed by a flood of newly ingested glucose and lipids if too large a meal is consumed (80, 85).

The most studied satiety signal is the duodenal peptide CCK, and it serves as an example. CCK is secreted from duodenal cells in response to nutrients in the lumen, with different specific nutrients being most effective in different species. Some of the secreted CCK enters the blood and stimulates the exocrine pancreas and liver/gallbladder to secrete appropriate enzymes into the duodenum to facilitate the digestive process. In 1973, Gibbs and colleagues (26) administered purified or synthetic CCK to rats before a meal and observed that it dose-dependently reduced the size of the meal. Since then, dozens of experiments have documented the ability of exogenous CCK to reduce meal size in numerous species including humans (31, 48, 50, 70). A role of endogenous CCK in eliciting satiety is indicated by the observation that the administration of specific CCK-1 receptor antagonists before a meal causes increased meal size in animals and humans (7, 30, 44, 56) and reduces the subjective feeling of satiety in humans (7).

Table 1. *Gastrointestinal peptides that influence food intake*

Reduce Meal Size	Increase Meal Size
CCK	Ghrelin
Bombesin family (bombesin, gastrin releasing peptide or GRP, and neuromedin B)	
Glucagon	
Glucagon-like peptide-1	
Glucagon-like peptide-2	
Apolipoprotein A-IV	
Amylin	
Somatostatin	
Enterostatin	
Peptide YY-(3–36)	

Although intravenous administration of CCK is efficacious in humans and nonhuman primates (21, 25, 50), it is most potent when administered either intraperitoneally or into arteries supplying the region of the upper duodenum in rats (14). CCK_1 receptors (formerly called CCK_A receptors) are expressed on sensory fibers of the vagus nerves innervating, among other areas, the tissue around the pyloric sphincter and the proximal duodenum (13, 42), and these fibers project to the NTS in the hindbrain.

The most popular conceptualization of the mechanism by which CCK works is that when nutrients enter the duodenum and stimulate CCK secretion, some of the CCK acts in a local paracrine manner to stimulate CCK_1 receptors on the sensory fibers of the vagus nerves (45, 49). Other branches of the same vagal sensory nerves emanate from the stomach wall and elsewhere, such that the same neurons can be sensitive to both CCK and other stimuli such as gastric distension (8). Hence, individual vagal neurons are able to integrate different kinds of signals relevant to ingestion, and electrophysiological recording studies as well as behavioral studies have found that the effect of a given dose of CCK is increased in the presence of stomach stretch (64, 65, 67). As discussed above, the CCK signal enters the hindbrain, where it initiates local reflexes and is relayed to the forebrain (48, 59). Disruption of the path at any point, whether by cutting the vagus nerves or by lesioning the NTS, renders CCK ineffective at reducing meal size (19, 49, 72, 73). CCK is an acutely acting signal, having a very short half-life (1–2 min). Related to this, administering it >15 min before the start of a meal is ineffective at reducing meal size (26).

A role for endogenous CCK in limiting the size of meals was demonstrated by the observation that antagonists to the CCK_1 receptor, when administered just before a meal, cause a larger meal to be consumed in animals (30, 44, 56) and humans (7).

An important, but as yet unanswered, question concerns the possibility that drugs that interact with CCK receptors and/or the receptors of other satiety-generating peptides might have therapeutic potential to treat obesity or eating disorders. Several types of experiments have addressed this possibility with CCK. When CCK is administered continuously, it rapidly becomes ineffective (15). When short-acting CCK is administered intermittently before the start of every spontaneous meal in rats, it continues to be effective at reducing meal size, but the animals compensate by eating more meals over days, and there is little impact on total daily food intake or body weight (78, 79). The implication is that humans given CCK therapeutically to reduce food intake also would compensate by increasing the number of meals they eat each day. In apparent contrast to this, rats with spontaneous mutations of the CCK_1 receptor (Otsuka Long Evans Tokushima Fatty rats) eat very large meals (46) and gradually gain weight over their lifetime (23), implying that a chronic absence of CCK signaling causes an increase in average meal size and has a small but cumulative effect on body weight over time in rats (9). That said, mice with a targeted deletion of the CCK_1 receptor have normal body weight (32), implying either that compensation for lack of CCK_1 signaling is different in rats and mice or that CCK is not involved in long-term body weight maintenance in mice. However, at present, no definitive conclusions can be reached regarding the possible therapeutic potential in humans of CCK analogs, especially long-acting analogs.

OTHER SATIETY SIGNALS

Besides CCK, gastrin-releasing peptide (GRP) (74), neuromedin B (33), enterostatin (54, 69), somatostatin (36), glucagon-like peptide-1 (GLP-1) (35, 51), apolipoprotein A-IV (22), and peptide YY-(3–36) [PYY-(3–36)] (6) are all peptides secreted from the gastrointestinal system that have been reported to reduce meal size when administered systemically. In addition, amylin (10, 37) and glucagon (24, 63), which are secreted from the pancreatic islets during meals, also reduce meal size (see Table 1).

CCK and other gastrointestinal signal-generating peptides are called satiety factors because their major action is to decrease meal size. An important issue is whether these same signals have a role in meal initiation. If so, it would suggest that tonic endogenous activity continuously compels animals to eat and that signals generated by food consumption and processing provide a brake that is activated mainly during meals. As the strength of the braking signal declines after meals, the omnipresent drive to eat gains predominance and meals are again initiated. Support for this hypothesis would be the finding that administration of satiety signals during an intermeal interval prolonged the time until the initiation of a subsequent meal. When administered to rats during the intermeal interval, CCK does not have this effect (26, 43). However, both bombesin and GRP increase the latency until a second meal is initiated (60, 61, 75, 76), implying that they might be normal controllers of meal onset.

In summary, when food is eaten, it interacts with receptors lining the stomach and intestine causing the release of peptides and other factors that coordinate the process of digestion with the particular food being consumed. Some of the peptides provide a signal to the nervous system, and as the integrated signal accumulates, it ultimately creates the sensation of fullness and contributes to cessation of eating. Administering the same peptides exogenously elicits a dose-dependent reduction of meal size, whereas administering antagonists (e.g., for CCK) or antisera (e.g., for apolipoprotein A-IV) causes increased meal size.

INTEGRATION OF SATIETY SIGNALS WITH ADIPOSITY SIGNALS

For the control system to be maximally efficient, the information from satiety signals must be integrated with signals related to a myriad of other factors including learning, the social situation, stress, and signals indicating total body fat (i.e., insulin and leptin). Although the nature of these interactions is not well understood, several generalizations or conclusions can be made. For one, the inhibitory signals related to body fat and meal ingestion can easily be overridden by environmental events. As an example, although satiety signals might indicate that no more food should be eaten during an ongoing meal, the sight, smell and perceived palatability of an offered dessert can stimulate further intake. Likewise, although an individual is severely underweight and ample food is available, the influence of stressors can preclude significant ingestion.

An important observation in recent years is that social, learned, and environmental controls over food intake, plus the adiposity signals insulin and leptin, act by changing the sensitivity to satiety signals. Consistent with this, administration of insulin or leptin changes the sensitivity to CCK. When an individual gains excess weight, more insulin and leptin are secreted and consequently stimulate the brain, rendering CCK more efficacious at reducing meal size (4, 38, 39, 58). An increased insulin signal in the brain also renders individuals more sensitive to the meal size-reducing action of amylin (62) and to the anorexigenic neuropeptide corticotropin-releasing hormone (57). As discussed above, the site of integration of satiety signals with other signals that influence meal size begins within individual vagal afferent fibers and continues into the hindbrain (47, 65, 66), where meal size is ultimately determined (27). At the same time, the arcuate nucleus continuously receives signals related to adiposity as well as information concerning ongoing meals from the hindbrain, and it also contains neurons that monitor ongoing metabolism directly (53), providing the hypothalamus with the capacity to integrate multiple signals that determine ingestion (1, 11, 20, 52, 68).

As a final point, two additional generalizations can be made regarding gastrointestinal peptides that contribute to satiety. The first is that most if not all of these peptides are also synthesized in areas of the brain involved in overall caloric homeostasis in addition to being made in the GI tract. This is true of CCK, bombesin-related peptides (GRP and NMB), GLP-1, apolipoprotein A-IV, and PYY-(3–36). The second is that with one exception, the net result of increased levels of any of these signals is a reduction in meal size. The exception is the recently described gastric peptide ghrelin, which is an agonist at the growth hormone secretagogue receptor. Ghrelin levels are increased after fasting and before meals (16), and administration of exogenous ghrelin causes large meals to be eaten (77, 86, 87). Similar to the satiety peptides, ghrelin is made in the brain as well as in the stomach, and there is evidence that the systemic ghrelin signal is carried in vagal afferent nerves to the brain (17).

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