Despite dramatic fluctuations in calorie intake, animals maintain a very stable body weight. The reason is that energy intake and expenditure are precisely matched. Long-term regulation of energy balance is dependent on the coordination and interpretation of signals such as those given by insulin and leptin indicating sufficient long-term energy stores as well as short-term, meal-related signals such as those given by cholecystokinin (CCK). Within the last 30 years, our knowledge of short-term signals has increased dramatically. Throughout the cephalo-caudal axis of the gastrointestinal system, discrete enteroendocrine cells respond to both mechanical and chemical stimulation. Meal-associated hormone release is dependent on the concentration and composition of the nutrients ingested. Released signals are transmitted neurally through vagal afferents or humorally as circulating ligands for specific receptor populations in the periphery and central nervous system. These signals are interpreted by the CNS and manifested as a behavioral modification of feeding. This review will present past and recent literature in support of gut hormones and their roles as mediators of satiety. Evidence from pharmacologic and physiologic studies involving both humans and rodents will be presented, along with a short section outlining the knowledge gained through the use of murine knockout models. Last, the contribution of satiety hormones as likely mediators of the effectiveness seen following obesity surgery will be reviewed. Although traditionally thought of as short-term, meal-related signals, enhanced, chronic hormone secretion and signaling resulting from gut reconstruction as seen with gastric bypass surgery most likely contributes to the superior efficacy of surgery as a treatment for obesity.

The central nervous system (CNS) receives information from the periphery relevant to an individual’s energy balance through metabolic, neural, and endocrine signals. The CNS in turn is able to integrate accurately and interpret these signals and subsequently direct information to controllers of energy intake and expenditure, including sending signals to numerous organs in the periphery, with the net outcome of these processes enabling the individual to maintain energy homeostasis over long periods of time. The long-term regulation of energy homeostasis and maintenance of a stable body weight are achieved through effective integration of signals indicating body fat stores, such as those given by insulin and leptin, with signals indicating immediately available energy as well as with signals indicating what is available from recently ingested food in the gastrointestinal tract.1-3 These short-term, meal-related signals, such as those given by cholecystokinin (CCK), are effective in maintaining appropriate meal size such that the daily regulation of energy intake is well coordinated with energy usage and long-term body weight.4,5

Gastrointestinal Signals Contributing to Energy Homeostasis

Dozens of hormonal and paracrine signals are known to be secreted from endocrine cells lining the gastrointestinal (GI) tract in response to the physicochemical properties of ingested food passing along the lumen. The term “hormone” was coined by Bayliss and Starling in 1902 when they isolated secretin from duodenal mucosa and observed that it stimulated pancreatic exocrine secretion.6 Two additional gastrointestinal hormones (gastrin7 and CCK8) were subsequently discovered and characterized, but it was not until the 1970s that significant progress in gastrointestinal endocrinology occurred, with over 40 novel hormones being discovered. Over the ensuing years came the important finding that many GI hormones are also expressed in the central nervous system (CNS)9 and that many of these are important signals that relay metabolic information between the GI tract and the brain.5,10-13

Gastrointestinal signals that influence the brain to stop an ongoing meal are collectively called satiety sig-
nals because, when they are administered exogenously, animals behave as if they are sated, ie, they eat smaller meals and engage in behaviors that normally occur when meals end.14-16 Humans given the same compounds also eat smaller meals and report that they are more sated.15,17-20 Although most GI-generated signals that influence meal size cause less food to be eaten, consistent with the term satiety signals, an exception has recently been discovered. Ghrelin is a peptide hormone made in the stomach, and, as discussed below, its administration causes more food to be eaten during meals.21,22

Satiety signals are released from specialized enteroendocrine cells that are interspersed among the gastric and intestinal cells lining the lumen of the GI tract (Figure 1).23 These enteroendocrine cells have finger-like extensions that project into the lumen and that contain chemoreceptors sensitive to nutrients and other constituents of the chyme or partially digested food as it progresses through the GI tract.24-27 Several different types of enteroendocrine cells have been identified and are categorized by the peptide signals that they synthesize and secrete, and Table 1 lists some of the important gastrointestinal-derived peptides involved in the control of food intake. Different enteroendocrine cells are sensitive to different classes of nutrients (eg, carbohydrates, fats, or proteins).27-32 The secretions of the enteroendocrine cells are mainly peptides, and they either enter the bloodstream and act as hormones or diffuse through the extracellular fluid to act in a paracrine fashion on nearby cells.24,33,34 The hormonal actions of these peptides are relatively well-known and involve actions at the liver,35 gallbladder,36 and pancreas37 as well as other organs38 (Figure 2). These are the actions that enable the proper mix of digestive enzymes to be added to the chyme to ensure optimal digestion. The paracrine actions of these same peptides comprise an area of intense investigation,35,34,39 and one model is depicted in Figure 2.

Afferent neurons innervate the gut, and some endings of their neurites are interspersed among the enteroendocrine cells.33,40 These nerve endings are thought to contain receptors for some of the peptide signals secreted in response to specific nutrients in the lumen. As an example, CCK secreted from intestinal I cells interacts with CCK-1 receptors (formerly called CCK-A receptors) on endings of sensory fibers of the vagus nerve, eliciting increased activity in the form of action potentials.13,41 The activated vagus in turn stimulates cells in the brainstem, eliciting reflexes that control GI function and sending signals to other brain areas that cause the individual to stop eating.12,13,42 Hence, satiety elicited by CCK and other GI peptides can be considered a neuroendocrine reflex. We consider it a reflex in part because CCK-mediated satiety exists in animals in which the hindbrain has been surgically disconnected from the forebrain.43 These chronically decerebrate animals, as they are called, do not initiate meals but will swallow liquid food that is slowly infused into their mouth and in this way consume normal-sized meals.44,45 These same animals eat (swallow) smaller meals when CCK is administered systemically, indicating that all components of the satiety reflex are contained within the hindbrain and peripheral nerves to the GI tract.43 Afferent fibers of the vagus nerve also express mechanoreceptors (stretch receptors) that are located on branches penetrating the musculature lining the GI tract.46,47 These receptors are sensitive to stomach and intestinal volume and luminal pressure, and increased pressure or volume in the stomach can result in the termination of a meal.48,49 This is presumably another important aspect of the satiety response. An intriguing recent observation is that the same vagal fibers have some

Table 1. Gastrointestinal Hormones That Affect Satiety

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Cell type</th>
<th>Effect on food intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCK</td>
<td>I</td>
<td>↓</td>
</tr>
<tr>
<td>Amylin</td>
<td>P</td>
<td>↓</td>
</tr>
<tr>
<td>GLP-1</td>
<td>L</td>
<td>↓</td>
</tr>
<tr>
<td>PYY (3-36)</td>
<td>L</td>
<td>↓</td>
</tr>
<tr>
<td>APO-AIV</td>
<td>Villus epithelia</td>
<td>↓</td>
</tr>
<tr>
<td>Enterostatin</td>
<td>Exocrine pancreas</td>
<td>↓</td>
</tr>
<tr>
<td>Bombesin/GRP</td>
<td>Stomach</td>
<td>↓</td>
</tr>
<tr>
<td>Oxyntomodulin</td>
<td>L</td>
<td>↓</td>
</tr>
<tr>
<td>Gastric leptin</td>
<td>Chief</td>
<td>↓</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>X/A-like</td>
<td>↑</td>
</tr>
</tbody>
</table>

NOTE. To date, the newly discovered hormone ghrelin is the only GI hormone known to increase food intake.
branches that express mechanoreceptors and are sensitive to volume and other branches that are located near enteroendocrine cells and could be sensitive to locally released GI peptides. This suggests that the same nerve fibers could be sensitive to both lumenal volume and lumenal contents. Support for this hypothesis is the observation that the same individual vagal fibers that respond to stretch by increasing their firing rate also increase their firing rate in response to CCK. This implies that different modes of sensory information are integrated within individual fibers innervating the GI tract. Information from the periphery generated by these signals is transmitted through direct contact with the central nervous system by circulating signals and also through stimulation of vagal afferents as recently reviewed. Accurate reception of these signals followed by the appropriate behavioral output by the central nervous system is vital to the maintenance of sufficient energy stores. The purpose of this review is to present current and vital information pertinent to the control of food intake for many of the established gastrointestinal signals. The role of structural manipulation of the gut during bariatric surgery will also be covered with an emphasis on the gastrointestinal hormone changes that result from these procedures.  

Cholecystokinin  

CCK is the most studied satiety signal and is secreted primarily in 2 forms, CCK-33 and CCK-8, from the I cells within the duodenal and jejunal mucosa. CCK is also synthesized within the central nervous system, primarily in the form of CCK-8. The 2 receptors that mediate the effects of CCK are termed CCK-1 and CCK-2, previously named CCK-A and CCK-B, respectively. The CCK-1 or A (for alimentary) receptor is primarily localized to the gastrointestinal system, whereas the CCK-2 or B (for brain) receptor is found within the CNS. CCK release from the intestine occurs in response to nutrient stimulation. Specifically, CCK is stimulated by fat and protein in the chyme, although the precise stimulants are species specific. Following its release, CCK elicits multiple effects on the gastrointestinal system, including the regulation of gut motility, contraction of the gallbladder, pancreatic enzyme secretion, gastric emptying, and gastric acid secretion. Most of these are thought to be due to endocrine actions of circulating CCK that has entered the bloodstream. Over 30 years ago, Gibbs et al first demonstrated that exogenous administration of either purified CCK or synthetic CCK-8 into the peritoneal cavity (ip) of rats reduced meal size. The response is dose dependent, with larger doses causing a greater reduction of food intake, and they observed that the CCK must be administered near the start of a meal to be effective. If CCK is administered more than 15 minutes before animals begin eating, it has no effect on meal size. The same group also observed that exogenous CCK elicited the same sequence of behaviors that noninjected rats display when they terminate meals. Centrally administered CCK also causes animals to consume smaller meals. The finding that exogenous CCK reduces meal size in rats has been replicated in many labs and extended to numerous species, including nonhuman primates and humans.
The observation that the administration of exogenous CCK reduces meal size, although consistent with the hypothesis that CCK is a natural satiety factor, is insufficient in and of itself to draw conclusions. Stronger evidence would be the demonstration that endogenous CCK, acting during normal meals, acts to limit caloric intake. Consistent with this, the administration of specific CCK-1 antagonists increases meal size in experimental animals and humans.1,7-10

Behavioral experiments indicate that CCK is truly a short-term, meal-reducing signal. This is illustrated by the fact that repeated or long-term chronic77 or intermittent76 administration of CCK to rats has no effect on weight loss. When the size of every meal is reduced by CCK, animals compensate by increasing meal frequency.76,77 Although the effects of exogenous CCK are brief, acting within the time of an ongoing meal, CCK also appears to interact with long-term signals of energy balance such as leptin and insulin.78 The anorectic effects of CCK can be augmented by the coadministration of subthreshold concentrations of leptin.79-82 Analogously, administering low doses of insulin directly into the brain also increases the satiating effect of CCK.83,84 Because leptin and insulin are important signals indicating the level of body fat to the brain,1,3,4,85 the implication is that body fat is regulated, at least in part, by changes in the sensitivity to meal-generated satiety signals such as those given by CCK. That is, if an individual loses body weight, the consequently reduced leptin and insulin signals in the brain would render the individual less sensitive to CCK, and there would be a tendency to eat larger meals; the opposite would occur if an individual were to gain body weight. When individuals are chronically obese, however, they are characterized with insulin and leptin resistance; hence, rats with hypothalamic obesity have hyperinsulinemia but a normal sensitivity to CCK’s satiating action,86 and fatty Zucker rats with genetic obesity have slightly reduced sensitivity to CCK.87 Although these forms of obesity are characterized with a blunted response to adiposity hormones, others are characterized by an absent response to CCK. Rats with a spontaneous mutation of the CCK-1 receptor (called OLETF rats88) eat slightly enlarged meals and gradually develop mild obesity over their lifetime.89,90

As discussed above, CCK is thought to interact with CCK-1 receptors on vagal sensory fibers, with the signal being relayed to the brainstem. Consistent with this, CCK’s anorectic effects can be eliminated by subdiaphragmatic vagotomy or selective damage to vagal afferent nerves.91,92 Likewise, lesions of the brainstem area that receives vagal sensory afferents attenuate CCK-elicited anorexia.93 Within the brain, recent data suggest that melanocortin-4 receptors (MC4) mediate CCK’s action.94

The Bombesin Family of Peptides

Exogenous administration of bombesin reduces meal size in animals and humans.18,95-96 Bombesin itself is an amphibian peptide, but gastrin releasing peptide (GRP) and neuromedin B (NMB) are mammalian analogs that reduce food intake when administered systemically to animals.97,98 Both GRP and NMB and their respective receptors are synthesized in the mammalian brain,99,100 and central administration of either peptide reduces food intake in rats.101 Consistent with the possibility that endogenous GRP and NMB reduce food intake, mice deficient for the GRP receptor do not suppress their food intake when administered either GRP or NMB, eat significantly large meals, and develop late-onset obesity.102

Most satiety factors such as CCK are thought to act by reducing the size of an ongoing meal. Hence, if they are administered between meals, they have no behavioral effects such as prolonging the time until the individual initiates a meal.52,103 Members of the bombesin family of peptides appear to be an interesting exception in that, when they are administered to animals between meals, they increase the amount of time until the subsequent meal begins.104-108

Amylin

Amylin, a peptide hormone secreted by pancreatic B cells in tandem with insulin secretion during meals, inhibits gastric emptying and gastric acid secretion.109Amylin causes a dose-dependent reduction of meal size when administered systemically110-112 or directly into the brain.113 In contrast to the effects of several other satiety peptides that reduce food intake by sending a signal to the brain via the vagus nerves, amylin appears to stimulate neurons in the area postrema of the brain directly.114-116 As is the case with CCK, the ability of amylin to reduce meal size is augmented in the presence of elevated adiposity signals such as those given by insulin.117

Glucagon-Like Peptide-1

Glucagon-like peptide-1 (GLP-1) is derived from posttranslational modification of the larger precursor molecule proglucagon.118 Proglucagon is synthesized within the endocrine L cells in the intestines, primarily the ileum and colon.118 The release of GLP-1 is elicited by both nutrient and neurohumoral stimulation from proximal regions of the small intestine, and a major action of GLP-1 is as an incretin, helping stimulate
insulin secretion during a meal.\textsuperscript{119-122} GLP-1 is secreted as GLP-1 (7-37) and GLP-1 (7-36).\textsuperscript{123} However, within a very short time (\~2 minutes), most plasma GLP-1 is degraded by the enzyme dipeptidyl-peptidase IV (DPP-IV), yielding the inactive analogs GLP-1 (9-36) and GLP-1 (9-37).\textsuperscript{123} The GLP-1 receptor (GLP-1r) is found in the periphery (gut and endocrine pancreas) and is widespread throughout the central nervous system.\textsuperscript{124}

The release of GLP-1 from the distal gut results from both direct and indirect mechanisms (for review see Brubaker and Anini\textsuperscript{125}). Although GLP-1 is rapidly secreted from the ileum during a meal, the process does not rely on actual nutrient contact with the endocrine L cells.\textsuperscript{126} Rather, the mechanism is thought to result from neural or humoral signals arising from the proximal intestine. Because GLP-1 inhibits gastrointestinal motility, reduces gastrointestinal secretions, and attenuates gastric emptying, it has been implicated as a major component of the “ileal brake,” an inhibitory feedback mechanism that regulates transit of nutrients through the course of the gastrointestinal tract.\textsuperscript{127,128}

GLP-1 also reduces food intake in animals and humans.\textsuperscript{129-135} The anorectic actions of GLP-1 are probably mediated through both peripheral and central mechanisms, and a population of neurons that synthesize GLP-1 is located in the brainstem and projects to hypothalamic and brainstem areas important in the control of energy homeostasis.\textsuperscript{136,137} In rats, central administration of GLP-1 dose dependently reduces food intake,\textsuperscript{134,135,138-140} an effect that is reversed by coadministration of the GLP-1 receptor antagonist exendin (9-39).\textsuperscript{130} Centrally administered GLP-1 reduces food intake through at least 2 mechanisms. GLP-1 receptors in the hypothalamus are thought to reduce intake by acting through the normal controls of caloric homeostasis.\textsuperscript{141-144} GLP-1 receptors in the amygdala, on the other hand, are thought to reduce food intake by eliciting symptoms of malaise and are presumably responsible for the conditioned taste aversions caused by GLP-1.\textsuperscript{134,141,145,146} It has recently been found that the receptors that trigger the satiety action of GLP-1 are located in the hypothalamus, whereas those that mediate malaise are in the amygdala.\textsuperscript{141} Kinzig et al observed that GLP-1 mediates both the endocrine and the behavioral responses to stress in rats,\textsuperscript{147} implying that the GLP-1 signal has complex actions, only some of which are directly relevant to the control of caloric homeostasis.

Peripheral administration of GLP-1 elicits satiety in healthy,\textsuperscript{133} obese,\textsuperscript{148} and diabetic humans.\textsuperscript{149,150} Because the half-life of active GLP-1 is less than 2 minutes, any direct effects are likely transient, and the reduction of food intake is most likely a result of GLP-1’s inhibitory effects on gastrointestinal transit and reduced gastric emptying.\textsuperscript{151} However, peripherally administered GLP-1 does cross the blood-brain barrier,\textsuperscript{152} such that its role and relative contribution within the CNS on food intake are not conclusive.

Because it both reduces food intake and stimulates insulin secretion, GLP-1 is a logical candidate as a therapeutic agent in the treatment of obesity and type-2 diabetes.\textsuperscript{153,154} However, as discussed above, a major problem in the potential use of GLP-1 as a treatment is its rapid degradation by DPP-IV. Hence, treatment strategies based on GLP-1 will likely use compounds that are not so rapidly destroyed, such as exendin-4, a 39-amino acid peptide originally isolated from the venom of the Gila monster salivary gland that shares 55% homology with GLP-1 (7-36).\textsuperscript{155,156} Exendin-4 is a potent agonist for the GLP-1 receptor and has a significantly greater half-life (\~30 minutes) than endogenous GLP-1.\textsuperscript{157} In animals and humans, exendin-4 has been demonstrated to reduce gastric emptying,\textsuperscript{139} lower fasting plasma glucose,\textsuperscript{158,159} and reduce food intake,\textsuperscript{158,160,161} supporting its potential use as a possible treatment for obesity and diabetes. An alternative strategy may be to utilize compounds that compromise DPP-IV, thus prolonging the half-life of endogenous GLP-1.

Glicentin, GLP-2, Oxyntomodulin, and Glucagon

Other peptides derived from proglucagon’s post-translational processing include glicentin, GLP-2, and oxyntomodulin as well as glucagon itself.\textsuperscript{118} Glicentin is involved in the inhibition of gastric acid secretion.\textsuperscript{162} It was recently reported by Dakin et al that, in the rat, neither intracerebroventricular injection nor direct application of glicentin to the hypothalamic paraventricular nucleus (PVN) reduced food intake.\textsuperscript{163} In contrast, that same group observed that oxyntomodulin does reduce food intake in the same paradigm.\textsuperscript{163} Although a specific receptor for oxyntomodulin has yet to be identified, it has been suggested that oxyntomodulin exerts its anorectic effects through the GLP-1r. This is supported by the finding that subthreshold doses of the GLP-1r antagonist, exendin (9-39), block both GLP-1 and oxyntomodulin-induced reductions in food intake.\textsuperscript{163} Long-term treatment with oxyntomodulin results in attenuated weight gain and a persistent decrease in food intake in rats.\textsuperscript{164} A more recent report by Dakin et al indicates that intravenous oxyntomodulin reduces caloric intake during a buffet meal and decreases hunger ratings in humans.\textsuperscript{165}

GLP-2 is best known for its beneficial role in intestinal adaptation and has become the focus of research on
GLP-2 and GLP-1 are highly similar in structure and are secreted in parallel from perfused ileal preparations. Therefore, a role for GLP-2 in the regulation of feeding seems logical. However, the participation of GLP-2 receptor in the regulation of food intake is controversial. Intracranial administration of GLP-2 reduces food intake in rats, but the effect can be blocked with a specific GLP-1 receptor antagonist. More recent studies in humans using both physiologic and pharmacologic doses of GLP-2 given intravenously had no effect.

Glucagon is the most widely studied peptide hormone cleaved from preproglucagon. It is secreted from both the endocrine pancreatic A cells and the distal intestine, and its best known action is to increase glucose secretion from the liver. Glucagon reduces meal size when administered systemically but not centrally. The signal being detected in the liver and relayed to the brain. A role for glucagon in the normal control of meal size was demonstrated by the observation that blocking the action of endogenous glucagon increases food intake. An authoritative review of proglucagon-derived peptides as potential candidates for the treatment of obesity has recently been made.

### Peptide Tyrosine-Tyrosine

Peptide tyrosine-tyrosine (PYY) is a member of the pancreatic polypeptide family that also includes pancreatic polypeptide (PP) and neuropeptide-Y (NPY). Like proglucagon-derived peptides, PYY is synthesized and secreted by L cells in the distal ileum and colon. In fact, most L cells that secrete GLP-1 also secrete PYY. PYY (1-36) and is degraded to PYY (3-36) by DPP-IV. Receptors that mediate the effects of PYY belong to the NPY receptor family and include Y1, Y2, Y4, and Y5. PYY (1-36) is an agonist for the Y1 and Y2 receptor and is a potent orexigen. Once PYY (3-36) is formed, it displays highly selective agonist activity for the Y2 receptor and has been reported to reduce food intake. The secretion of PYY from the gut is proportional to the caloric density of the ingested nutrients with lipids and carbohydrates being the primary nutrients in the stimulation of PYY release.

Like GLP-1, PYY has been implicated as a major component of the ileal brake. Its secretion can be stimulated by the presence of nutrients, particularly lipids, within the ileum itself or else prior to direct nutrient contact because of neurohumoral signals originating from the proximal gut. Pharmacologic experiments have yielded conflicting results regarding PYY as a satiety signal. Several reports indicate that PYY is an orexigenic peptide, with feeding stimulatory properties superior to those of neuropeptide-Y (for review see Hagan). This is particularly the case when PYY is administered directly into the cerebral ventricles. In contrast, it was recently reported that peripheral administration of PYY (3-36) reduces food intake in rodents, nonhuman primates, and humans. The modest decrease of food intake has been replicated in monkeys but not in rats.

It has been hypothesized that PYY influences food intake through its interaction with Y2 receptors in the hypothalamic arcuate nucleus. The arcuate nucleus is a major conduit for feeding-related signals. The model is that circulating PYY gains access to the brain as it freely crosses the blood-brain barrier.

### Gastric Leptin

Leptin was first described as a gene product from adipose tissue, which plays an important role in the central regulation of food intake and energy balance. Extra-adipose sites have now been identified that synthesize and secrete leptin, including the placenta, skeletal muscle, and the stomach. The production of leptin within the stomach is localized to the fundic glands, specifically the P cells and pepsinogen-secreting chief cells. The presence of leptin within both of these cell types suggests that gastric leptin possesses both exocrine and endocrine functions, and it has been estimated that up to 25% of circulating leptin actually derives from the stomach.

Studies in humans and animals indicate that gastric leptin is regulated by energy state. During fasting, gastric leptin synthesis is reduced, and a brief period of refeeding is capable of emptying all the leptin stores within the stomach of the rat. Leptin synthesis is also regulated by other gut peptides, including CCK, secretin, and pentagastrin. Leptin synthesis in the gastric mucosal cells, and CCK administration increases leptin synthesis and release from gastric chief cells. Insulin increases gastric leptin secretion into the lumen of the stomach in humans. This effect appears to be vagally mediated because vagotomy abolishes the response. Pentagastrin-induced leptin secretion, on the other hand, is not influenced by vagotomy. The ability of circulating leptin to reduce food intake and body weight is well-known, and several reviews exist.
central regulation of energy homeostasis via receptors in the arcuate nucleus and elsewhere in the brain.214

Apolipoprotein A-IV

Apolipoprotein A-IV (apo A-IV) is a large peptide synthesized by intestinal cells during the packaging of digested lipids into chylomicrons that subsequently enter the blood via the lymphatic system.215 Apo A-IV is also synthesized in the arcuate nucleus.216 Systemic or central administration of apo A-IV reduces food intake and body weight of rats,217 and administration of apo A-IV antibodies has the opposite effect.218 Because both intestinal and hypothalamic apo A-IV are regulated by absorption of lipid but not carbohydrate,219 this peptide may be an important link between short- and long-term regulators of body fat (see review by Tso et al217). A second digestion-related peptide, enterostatin, is also closely tied to lipid digestion. When ingested fat enters the intestine, the exocrine pancreas secretes lipase and colipase to aid in the digestive process; enterostatin is a cleavage by-product of the formation of colipase from pro-colipase. Administration of exogenous enterostatin either systemically220,221 or directly into the brain222 reduces food intake, and, when rats are given a choice of foods to eat, the reduction is specific for fats; that is, enterostatin does not decrease the intake of carbohydrates or proteins.223 Therefore, 2 peptides that are secreted from the gut during the digestion and absorption of lipids, apo A-IV and enterostatin, act as signals that decrease food intake, and at least one of them selectively reduces the intake of fat. Macronutrient specificity has not been assessed with apo A-IV.

Ghrelin

Although not a gastrointestinal satiety hormone, ghrelin must be included in any discussion of gut hormones that influence food intake. Ghrelin is synthesized and secreted from the fundic region of the stomach and has been identified as the endogenous ligand for the growth hormone secretagogue receptor. Fasting increases plasma levels of ghrelin,224 and exogenous ghrelin exhibits potent orexigenic properties when administered peripherally or centrally.225 Ghrelin has also been linked to the anticipatory aspects of meal ingestion because levels peak shortly before scheduled meals in humans and rats224 and fall shortly after meals end, and high plasma ghrelin has been linked to the hyperphagia and obesity of individuals with the Prader Willi syndrome.227

An intriguing question concerns why there is such a large imbalance in the gastrointestinal peptides that influence food intake, ie, whereas numerous peptides secreted from the stomach and intestines decrease food intake, only one, ghrelin, increases it. One possibility relates to the phenomenon of satiety. Meals are generally stopped long before any physical limit of the stomach is reached. This is easily demonstrated when food is diluted with noncaloric bulk and animals increase the volume of food consumed to attain the same caloric load.228 It has therefore been argued that a major function of satiety signals is to prevent the consumption of too many calories at one time, lest too great an increase of postprandial blood glucose and other nutrients occurs.230 That is, as the gastrointestinal tract detects the various macronutrients consumed as a meal is being eaten, the secretions that it makes to coordinate the digestive process also reflect the quantity of nutrients that will soon be entering the blood and thereby constitute a behavioral brake to the eating process. This is presumably complementary to the ileal brake that slows gastric emptying and consequently also limits the rate at which absorbed nutrients enter the blood.

Relationship Between Gastrointestinal and Brain Signals That Influence Food Intake

An important principle is that many of the peptides that are made in the gastrointestinal system and influence food intake are also synthesized in the brain. This includes CCK, GLP-1, apolipoprotein A-IV, gastrin-releasing peptide, neuromedin B, PYY, and ghrelin. Apparent exceptions are the pancreatic hormones insulin, glucagon, and amylin and the adipose tissue/stomach hormone leptin. The fact that so many peripheral signals are also synthesized locally in the brain raises the question of whether and how the same signals secreted from different places in the body interact. A simple generalization is that, if a peptide reduces (or increases) food intake when administered systemically, it probably has the same action when administered centrally. With regard to changes of food intake, this is true of CCK,63,64 GLP-1,134,135,138-140 apolipoprotein A-IV,217 gastrin-releasing peptide,101 neuromedin B,101 and ghrelin.22 PYY is a possible exception in that it reportedly decreases food intake when administered systemically185 but increases it when administered directly into the brain.184,191-195 Another confounding observation is that peptide signals that are not synthesized in the brain nonetheless have the same effect on food intake when administered directly into the brain. This is true of leptin232,233 as well as the pancreatic hormones insulin175 and amylin113 but not glucagon.175 Because specific receptors for each of these hormones exist on
neurons in the brain,85 the implication is that molecules in the circulation are able to circumvent the blood-brain barrier. This could occur by any of several means, including selective transport systems through capillary endothelial cells as has been described for insulin and leptin, interaction with neuronal receptors in brain areas with a relaxed or absent blood-brain barrier as has been described for amylin, or by being sufficiently small or lipophilic to penetrate the barrier in small amounts (see reviews in Banks235 and Woods et al236).

There are other complexities of the peripheral-central dichotomy. GLP-1 is synthesized in the ileum as well as in the brainstem, and it reduces food intake when administered either systemically or centrally. However, when administered directly into the brain, the reduction of food intake occurs for different reasons in different specific areas. Kinzig et al141 found that the anorexia caused by GLP-1 in the amygdala is secondary to a sensation of visceral illness, whereas the anorexia elicited by GLP-1 in the hypothalamus appears to mimic what occurs in natural satiety.

**Knockout Mice and Natural Mutations**

Because the gastrointestinal signals that govern food intake are components of a complex integrated and redundant control system, it is not surprising that knockout models often provide inconclusive information as to a peptide’s contribution to the regulation of feeding.237 To use CCK as an example and as discussed above, considerable evidence implicates CCK as an acutely acting satiety signal. Consistent with this, genetically engineered mice lacking CCK-1 receptors are insensitive to the anorexic action of CCK, and they have a normal body weight.238 This is consistent with the observation that, when rats are administered exogenous CCK prior to every meal, they do not lose weight despite receiving 20 or more injections of CCK each day.76 In contrast to what is observed in mice lacking CCK-1 receptors and as discussed above, OLETF rats lacking a functional CCK-1 receptor develop obesity over their lifetime.89,90 Hence, either there are fundamental species differences in the impact of CCK on body weight or there are subtle differences between the natural and the engineered animal lacking functional CCK-1 receptors.

As another example, despite the apparent role of GLP-1 in the control of food intake and glucose homeostasis as discussed above, GLP-1 receptor knockout mice have normal body weight, implying that GLP-1 signaling is not essential for the long-term control of energy homeostasis. These mice do, however, develop diabetes, thus emphasizing the critical importance for GLP-1 in the maintenance of pancreatic function.239-241 Analogously, ghrelin-deficient mice have no obvious behavioral or metabolic phenotype and are indistinguishable from wild-type littermates.242 Glucagon inhibitory peptide (GIP) is secreted from intestinal K cells within the duodenal mucosa. Although exogenous GIP administration does not alter food intake,243 GIP is an incretin that, like GLP-1, is important in glucose homeostasis.244 Interestingly, the generation of GIP receptor knockout mice revealed previously unidentified roles for GIP as an important regulator of energy balance. GIP knockout mice are resistant to diet-induced obesity and, when crossed with ob/ob or leptin-deficient mice, cause a reduction in body weight.245 GIPR-deficient mice also have increased energy expenditure when exposed to diets high in fat.245 Given that GIP receptors are found on the adipocyte, these findings are consistent with a role for GIP in the regulation of body fat stores. Last, some phenotypes of other GI peptide knockout mice are quite consistent with the peptides’ described physiologic role, such as the GRP receptor-deficient mice (as mentioned above). These mice eat large meals, become obese, and do not reduce their food intake when given GRP or NMB.102

**Effect of Obesity Surgery on Gut Hormones**

Surgery is the most effective treatment for morbid obesity, with the most successful surgeries involving a substantial restructuring of the stomach and/or the small intestines. The contemporarily most commonly performed surgery, the Roux-en-Y gastric bypass, involves both restrictive and malabsorptive features. In this procedure, the stomach volume is minimized to hold $\leq 50\text{ mL}$ while the small intestines are attached proximal to the pylorus, allowing for rapid delivery of stomach contents to the small intestine (Figure 3B). Additionally, a considerable segment of small intestine is bypassed, resulting in a much shorter gastrointestinal tract. Developed by Mason and Ito in 1967,246 the Roux-en-Y has proven to be effective in reducing body weight and is associated with relatively few complications compared with jejunoileal bypass (JIB) procedure, which involved bypassing nearly 90% of the small intestine (Figure 3A)247 and caused severe malabsorption.

Although the obvious contribution of restriction and malabsorption was recognized when various bariatric surgeries were being developed, not so obvious were the resulting changes in endocrine signals arising within the gastrointestinal tract. Changes in these signals have re-
cently become recognized as likely contributors to the weight loss following surgery. The hypothesis is that enhanced or premature nutrient stimulation of distal segments of the intestines causes increased secretion of intestinal peptides that function as satiety signals and that this may be sufficient to induce weight loss, independent of any malabsorption or restriction. Several studies have documented changes in gastrointestinal hormones following bariatric surgery (Table 2). Twenty years following jejunoileal bypass, patients had significantly enhanced CCK, enteroglucagon, and peptide YY levels. Gastric bypass and biliopancreatic diversion also resulted in increased plasma enteroglucagon. These findings therefore support a role for gut hormones as potentially important mediators in the hypophagia and weight-reducing effects of bariatric surgery. Furthermore, patients who were presurgically type 2 diabetic often have rapid improvements in glucose homeostasis (for review see Greenway et al). Although this effect could be solely a consequence of weight loss following surgery, improvements in fasting glucose have been documented within days following surgery, with many patients becoming medication free within weeks (for review see Rubino and Gagner). It is reasonable to speculate that the increased secretion of incretins such as GLP-1 and GIP following surgery are at least partly responsible for these improvements.

One surgical model that supports the hypothesis that increased intestinal hormones alone may act as mediators of weight loss and reduced food intake is ileal transposition. First designed in 1981 to isolate the effects of distal gut stimulation in the absence of malabsorption and restriction, ileal transposition has only been systematically investigated in the laboratory rat. This procedure involves the transposition of an isolated segment (10-20 cm) of distal ileum-jejunum carrying full vasculature and innervation to the duodeno-jejunal region. The results of ileal transposition surgery are that rats eat less and lose weight following the procedure and have significant increases in the secretion and synthesis of distal gut hormones such as PYY and GLP-1. These findings are consistent with the hypothesis that augmented levels of intestinal hormones independently regulate body weight and food intake.

Table 2. Effects of Bariatric Surgery on Gastrointestinal Intestinal Hormones

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Hormone</th>
<th>Change</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric bypass (Roux-en-Y)</td>
<td>Ghrelin</td>
<td>↓</td>
<td>263</td>
</tr>
<tr>
<td>Gastric banding</td>
<td>Ghrelin</td>
<td>↑</td>
<td>265</td>
</tr>
<tr>
<td>Vertical-banded Gastroplasty</td>
<td>Ghrelin</td>
<td>↓</td>
<td>266</td>
</tr>
<tr>
<td>Biliopancreatic diversion/duodenal switch</td>
<td>Enteroglucagon</td>
<td>↑</td>
<td>271</td>
</tr>
<tr>
<td>Jejunoileal bypass</td>
<td>CCK</td>
<td>↑</td>
<td>251</td>
</tr>
<tr>
<td></td>
<td>GLP-1</td>
<td>↑ (ns)</td>
<td>274</td>
</tr>
</tbody>
</table>

Figure 3. Restrictive and malabsorptive bariatric surgeries. The mechanisms underlying bariatric surgeries range from being primarily malabsorptive, such as occurs with the (A) jejunoileal bypass, to completely restrictive as in (D) vertical banded gastroplasty. Surgeries including the (B) Roux-en-Y gastric bypass and (C) biliopancreatic diversion use a combination of restrictive and malabsorptive components.
Effects of Bariatric Surgery on Plasma Ghrelin

The initial report by Cummings et al. that, following gastric bypass, circulating ghrelin is drastically diminished has led to intense investigation into a possible role of ghrelin in the effects of obesity surgery. In contrast to what occurs after gastric bypass, plasma ghrelin normally increases following nonsurgical weight loss and is proportional to lean body mass. Hence, a reduction of ghrelin, and a consequent reduced stimulant for food intake, might well contribute to the weight loss of gastric bypass surgery. Initially, it was proposed that the exclusion of the fundus region of the stomach, the site that produces the majority of circulating ghrelin, was the mechanism through which gastric bypass resulted in lower ghrelin levels. However, numerous follow-up studies have either contradicted such findings or reported no change in ghrelin following surgery (Table 2). Normally, ghrelin levels rise prior to or in preparation for a meal and decline immediately postprandially. To examine the contribution of the stomach in this response, Williams et al examined whether distension of the stomach and/or nutrient stimulation were required for the prandial changes in plasma ghrelin. Only when the infused calories (glucose) were allowed to pass through the pylorus into the foregut did ghrelin levels change, indicating that postgastric feedback is necessary for changes in ghrelin to occur postprandially. No changes in ghrelin were seen when glucose was held in the stomach by use of a pyloric cuff. Furthermore, infusion of nutrients directly into the foregut is just as effective in suppressing ghrelin as is nutrient administration into the stomach. These findings argue against the hypothesis that exclusion of the stomach lumen from ingested nutrients is the cause of reduced ghrelin following gastric bypass surgery. More investigation is required to determine the mechanisms underlying changes in ghrelin secretion following gastric bypass surgery.

Summary

We have reviewed what is known of the gastrointestinal and related peptide signals that influence food intake, including what is known of their mechanism of action. Several generalities can be made. The first is that the majority of these signals act to reduce the intake of further calories, effectively categorizing them as satiety signals. The lone exception is ghrelin, and its endogenous function is not yet well established. The second point is that there are many different satiety signals and that these are released as chyme or other stimuli that interact with all levels of the gastrointestinal tract from the stomach to the ileum. Different signals are released in response to different nutrients that have been ingested. Another generalization is that the information carried in satiety signals reaches the brain posteriorly, either being conveyed in the vagus nerve or entering the hindbrain directly. This is in contrast to adiposity signals such as insulin and leptin that enter the brain at the level of the hypothalamus. For the most part, satiety signals work by stopping meals once they have begun as opposed to delaying the onset of eating. A final point is that one reason certain types of intestinal bypass surgery is successful at reducing food intake and causing weight loss may be related to enhanced secretion of satiety signals.

References


185. Taylor RG, Bevenidige DJ, Fuller PJ. Expression of ileal glucagon and peptide tyrosine-tyrosine genes. Response to inhibition of


