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Central Control of Body Weight and Appetite

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Context: Energy balance is critical for survival and health, and control of food intake is an integral part of this process. This report reviews hormonal signals that influence food intake and their clinical applications.

Evidence Acquisition: A relatively novel insight is that satiation signals that control meal size and adiposity signals that signify the amount of body fat are distinct and interact in the hypothalamus and elsewhere to control energy homeostasis. This review focuses upon recent literature addressing the integration of satiation and adiposity signals and therapeutic implications for treatment of obesity.

Evidence Synthesis: During meals, signals such as cholecystokinin arise primarily from the GI tract to cause satiation and meal termination; signals secreted in proportion to body fat such as insulin and leptin interact with satiation signals and provide effective regulation by dictating meal size to amounts that are appropriate for body fatness, or stored energy. Although satiation and adiposity signals are myriad and redundant and reduce food intake, there are few known orexigenic signals; thus, initiation of meals is not subject to the degree of homeostatic regulation that cessation of eating is. There are now drugs available that act through receptors for satiation factors and which cause weight loss, demonstrating that this system is amenable to manipulation for therapeutic goals.

Conclusions: Although progress on effective medical therapies for obesity has been relatively slow in coming, advances in understanding the central regulation of food intake may ultimately be turned into useful treatment options. (J Clin Endocrinol Metab 93: S37–S50, 2008)

The past decade has seen an increasing recognition that a complex interplay exists between the central nervous system (CNS) and the activity of numerous organs involved in energy homeostasis. This requires the transmission of key information to the brain, and control of food intake is one component of energy balance where endocrine signaling from the periphery to the CNS has a particularly important role. Considered broadly, energy homeostasis consists of the interrelated processes integrated by the brain to maintain energy stores at appropriate levels for given environmental conditions. Energy homeostasis thus includes the regulation of nutrient levels in key storage organs (e.g. fat in adipose tissue and glycogen in the liver and elsewhere) as well as in the blood (e.g. blood glucose). To accomplish this, the brain receives continuous information about energy stores and fluxes in critical organs, about food that is being eaten and absorbed, and about basal and situational energy needs by tissues. The brain in turn controls tissues that have important roles in energy homeostasis, like the liver and musculoskeletal system, as well as the secretion of key metabolically active hormones, primarily through the autonomic nervous system. The brain is thus able to respond to ongoing as well as unanticipated demands via well-coordinated responses to prevent shortfalls in energy stores while maintaining biochemical homeostasis. This review focuses on hormonal and related signals that inform the brain of energy levels, thereby influencing energy intake and ultimately body weight.

As a general rule, signals arising in the periphery that influence food intake and energy expenditure can be partitioned into two broad categories (Fig. 1) (1–3). One comprises the signals generated during meals that cause satiation (i.e. feelings of fullness), and the other comprises the signals arising from the body’s metabolic state that influence the initiation of feeding (i.e. hunger). These two types of signals are largely distinguished by their temporal relationship to meals, with satiation signals arising primarily during meals and orexigenic signals associated with basal metabolic needs.

Abbreviations: AgRP, Agouti-related peptide; apo A-IV, Apolipoprotein A-IV; ARC, arcuate nucleus; CCK, cholecystokinin; DPP-IV, dipeptidyl peptidase IV; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GLP-1r, GLP-1 receptor; GRP, gastrin-releasing peptide; LHA, lateral hypothalamic area; MC3R, melanocortin 3 receptor; MC4R, melanocortin 4 receptor; α-MSH, α-melanocyte-stimulating hormone; NMB, neuropeptide B; NPY, neuropeptide-Y; POMC, proopiomelanocortin; PYY, peptide tyrosine-tyrosine.
ness that contribute to the decision to stop eating) and/or satiety (i.e., prolongation of the interval until hunger or a drive to eat reappears). The prototypical satiation signal is the duodenal peptide cholecystokinin (CCK), which is secreted in response to dietary lipid or protein and which activates receptors on local sensory nerves in the duodenum, sending a message to the brain via the vagus nerve that contributes to satiation. The second category includes hormones such as insulin and leptin that are secreted in proportion to the amount of fat in the body. These “adiposity” hormones enter the brain by transport through the blood-brain barrier and interact with specific neuronal receptors primarily in the hypothalamus to affect energy balance. Satiation and adiposity signals interact with other factors in the hypothalamus and elsewhere in the brain to control appetite and body weight, and they are the topic of this review.

Body weight (adiposity) is a homeostatically regulated variable, and its long-term maintenance can only occur via a close linkage of energy intake to energy expenditure. This means that over long intervals, the amount of food consumed must provide energy equivalent to the amount of energy expended. Humans and most mammals acquire energy in discrete episodes or meals. For many modern-day humans, the impetus to begin a meal is rarely if ever based on a biological deficit or need such as insufficient glucose. Rather, “appetite” and “hunger” occur, and meals are initiated based on habit, time of day, specific social situations, convenience, or stress, factors that are not linked to energy needs and so are nonhomeostatic (4–6). Arguably, this has been the case throughout human evolution as well, with the initiation of feeding governed by nonhomeostatic factors such as food availability or having a safe haven to eat. Thus, the homeostatic influence over food intake is often left to the control over how many calories are consumed once a meal begins; i.e., on meal size. Consistent with this, many of the secretions of the gastrointestinal (GI) tract during a meal, such as CCK, are proportional to the number of calories consumed, and some of these secretions function as satiation signals to the CNS to help limit meal size (see reviews in Refs. 7–9).

In contrast to satiation signals that are phasically secreted during meals, adiposity signals are more tonically active, providing an ongoing message to the brain proportional to total body fat. Insulin is tonically secreted in basal amounts, with phasic increments occurring during meals, and both components of total insulin secretion (i.e., basal and meal-stimulated) are directly proportional to body fat (10). Leptin is secreted in direct proportion to body adiposity, following a diurnal pattern with less direct connection to meals than insulin (11). As an individual changes body weight through caloric restriction or overeating, the amounts of insulin and leptin secreted into the blood change in parallel, and this in turn is reflected as an altered signal of body fatness, tantamount to body energy stores, reaching the brain (1–3). These adiposity signals interact with anabolic and catabolic neural circuits, causing a change in sensitivity of the brain to satiation signals. For example, during food deprivation or dieting, reduced brain insulin/leptin signaling renders neural cir-

**FIG. 1.** Model summarizing different levels of control over energy homeostasis. During meals, signals such as CCK, GLP-1, and distension of the stomach that arise from the gut (stomach and intestine) trigger nerve impulses in sensory nerves traveling to the hindbrain. These satiation signals synapse with neurons in the nucleus of the solitary tract (NTS) where they influence meal size. Ghrelin from the stomach both acts on the vagus nerve and stimulates neurons in the ARC directly. Signals related to body fat content such as leptin and insulin, collectively called adiposity signals, circulate in the blood to the brain. They pass through the blood-brain barrier in the region of the ARC and interact with neurons that synthesize POMC or NPY and AgRP. ARC neurons in turn project to other hypothalamic areas including the PVN and the LHA. The net output of the PVN is catabolic and enhances the potency of satiation signals in the hindbrain. The net output of the LHA, on the other hand, is anabolic, suppressing the activity of the satiation signals. In this way body fat content tends to remain relatively constant over long intervals by means of changes of meal size.
cuits controlling meal size less sensitive to satiation signals such as CCK. As a consequence, the homeostatic setting is geared for the intake of larger meals because more food must be consumed before a sufficient satiation signal is generated to stop eating. This situation of extra-large meals persists until body weight (and hence the insulin/leptin signal) returns to normal. Conversely, after excessive weight gain, the increased insulin/leptin brain signal results in increased sensitivity to satiation signals, and smaller meals are consumed until the excess weight is lost. A major dilemma facing clinicians and others involved in public health is the slippage in the latter limb of this homeostatic system that permits excessive energy storage, obesity, and the associated diseases of nutritional excess; e.g. diabetes, cardiovascular disease, and some cancers.

**Satiation Signals**

By definition, satiation factors, when administered to humans or animals at the start of a meal, result in a smaller-than-normal meal being consumed. Exogenously administered satiation factors, or endogenous secretion of these compounds, activates specific receptors that cause premature cessation of eating. There are several excellent reviews of satiation signals such that only the salient points need to be reviewed here (7–9, 12–14). It is generally accepted that for an endogenous compound to be considered a satiation signal, it is secreted in response to food ingestion, acts within the time frame of a single meal, reduces meal size without creating malaise or incapacitation, and is effective at physiological doses, and removing or antagonizing its endogenous activity increases meal size (7, 15).

The best-established satiation signals are secreted from specialized enteroendocrine cells in the wall of the GI tract in response to the digestion and absorption of meals. In the classic model of satiation, local sensory nerves express receptors for these gut peptides as they are secreted such that the brain is immediately informed about the nutritional content of the meal by monitoring the level of hormones secreted to cope with it. As a complex meal is consumed, the mix of macronutrients (carbohydrates, fats, and proteins) stimulates a proportional blend of satiation peptides, and an overall message indicating meal content is integrated in the hindbrain where it activates appropriate responses, including ultimately cessation of the meal. In humans, this is associated with a sensation of fullness. Although not all intestinal hormones double as satiation signals, they all presum-ably contribute to the assimilation of nutrients; i.e. by stimulating the secretion of appropriate enzymes, water, and other compounds into the lumen of the gut and regulating GI motility. Table 1 provides a list of GI and other meal-related hormones/peptides that are generally considered to be satiation signals.

**Cholecystokinin**

CCK was the compound first identified to fit the criteria for a satiation factor, so that much is known about its actions. Consequently, CCK has become the model for the larger class of satiation factors. When food containing fat or protein is consumed and enters the duodenum, CCK is secreted from I cells.

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**TABLE 1. GI hormones that affect satiation**

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Effect on food intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCK</td>
<td>Decrease</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Decrease</td>
</tr>
<tr>
<td>PYY</td>
<td>Decrease</td>
</tr>
<tr>
<td>Ago A-IV</td>
<td>Decrease</td>
</tr>
<tr>
<td>Enterostatin</td>
<td>Decrease</td>
</tr>
<tr>
<td>Bombesin/GRP/NMB</td>
<td>Decrease</td>
</tr>
<tr>
<td>Oxyntomodulin</td>
<td>Decrease</td>
</tr>
<tr>
<td>Amylin</td>
<td>Decrease</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Increase</td>
</tr>
</tbody>
</table>

CCK enters the blood and has hormonal influences on gut motility, contraction of the gallbladder, pancreatic enzyme secretion, gastric emptying, and gastric acid secretion (16–19). However, CCK also diffuses locally to provide a paracrine stimulus to CCK-1 receptors on nearby branches of vagal sensory nerves (20–23). Through this mechanism a message, generally that ingested fat/protein is being processed and will soon be absorbed, is conveyed to the hindbrain and relayed to the hypothalamus where it is integrated into the composite information on energy homeostasis (20, 24–28) (Fig. 2).

The decrease of meal size elicited by exogenous CCK is dose-dependent, with higher doses causing greater reductions of meal size. However, CCK does not prevent meals from occurring; rather, it decreases the size of the meal once it has begun, reducing hunger and increasing fullness without concomitant sensations of illness or malaise. When a CCK-1 receptor antagonist is administered before the presentation of food to animals or humans, larger-than-normal meals are consumed (29–31), providing compelling evidence that endogenous CCK normally acts to sup-

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**FIG. 2. Satiation signals arising in the GI system converge on the dorsal hindbrain (D) where they are integrated with taste and other inputs. The dorsal hindbrain makes direct connections with the ventral hindbrain (V) where neural circuits direct the autonomic nervous system to influence blood glucose and where the motor control over eating behavior is located. The dorsal hindbrain also conveys information on satiation and adiposity signals as well as available nutrients with experience, the social situation and stressors, and with time of day and other factors. The integrated information is then conveyed posteriorly back to the ventral hindbrain as well as to the pituitary to influence all aspects of energy homeostasis. Animals lacking neural connections between the hindbrain and the hypothalamus reduce the intake of individual bouts of eating when the stomach is distended or they are administered CCK. However, those animals cannot regulate their body weight and are not sensitive to past experience, time of day, or social factors (243).**
Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is derived from proglucagon in intestinal L cells that are most prevalent in the ileum and colon (39). GLP-1 secretion is elicited by nutrients, but the mechanism whereby the distal L cells are stimulated early within meals may require neurohumoral signals initiated in the proximal regions of the small intestine (40). GLP-1 has a broad range of actions on glucose metabolism (41), most prominently stimulation of insulin secretion, but also inhibition of glucagon release. Because GLP-1 inhibits glucose production and secretion, 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 GI tract (42, 43). It has generally been assumed that GLP-1 mediates these various actions through an endocrine mechanism, by binding directly to key target tissues like pancreatic islet cells. However, this mechanism has recently been called into question, in large part because GLP-1 is rapidly metabolized in the circulation by the protease dipeptidyl peptidase IV (DPP-IV) (44). Indeed, the half-life of GLP-1 in human plasma is only 1–2 min, and the product of DPP-IV action, a truncated GLP-1, is inactive with regard to glucose metabolism (45). Because the GLP-1 receptor (GLP-1r) is expressed by peripheral and CNS neurons as well as by cells in the pancreatic islets and the GI tract, recent attention has focused on neural mechanisms of GLP-1 action (46–48).

GLP-1 administration reduces food intake in animals and humans (49–54), and these anorectic actions are thought to be mediated through both peripheral and central mechanisms. A population of neurons that synthesize GLP-1 is located in the brain stem and projects to hypothalamic and brain stem areas important in the control of energy homeostasis (55, 56). Centrally administered GLP-1 reduces food intake through at least two mechanisms. GLP-1r in the hypothalamus appears to reduce intake by acting on caloric homeostatic circuits (57–60), whereas GLP-1r in the amygdala reduce food intake by eliciting symptoms of stress or malaise (61, 62).

Systemically administered GLP-1 elicits satiation in healthy (53), obese (63), and diabetic (64, 65) humans. Because the half-life of active GLP-1 is less than 2 min, any direct effects are likely transient, and the reduction of food intake may result from inhibitory effects of GLP-1 on GI transit and reduced gastric emptying (66). However, peripherally administered GLP-1 does cross the blood-brain barrier (67), perhaps enabling circulating GLP-1 to interact with the brain GLP-1r. Because it both reduces food intake and stimulates insulin secretion, the GLP-1 system has been adapted to the treatment of type 2 diabetes (68, 69). DPP-IV-resistant, long-acting GLP-1r agonists are effective at reducing blood glucose in persons with type 2 diabetes and also cause weight loss (70). In addition, inhibitors of DPP-IV, which elevate endogenous GLP-1 levels, are also effective at improving glycemic control in diabetic patients (71, 72).

The effect of chronic GLP-1r agonists to cause weight loss is not consistent with the general principle that satiation peptides are subservient to long-term regulators of energy balance, such as leptin (3). One potential explanation is that because GLP-1 can activate nonhomeostatic pathways that suppress food intake and otherwise reduce body weight, the effects of chronic administration of GLP-1r agonists work around the homeostatic systems controlling body weight. Indeed, nausea, a hallmark feature of nonhomeostatic anorexia, is very common with GLP-1r agonist treatment (73), although this response wanes with continued treatment and is not present in all persons who lose weight. Another possible explanation for why patients treated with indigestible GLP-1r agonists lose weight is that repeated pharmacological doses of a satiation signal can overcome homeostatic restraints. Consistent with this hypothesis is the failure of DPP-IV inhibitor treatment, which has a smaller effect to raise circulating concentrations of GLP-1r agonist activity than do injectable GLP-1 mimetics to cause weight loss. Although it is not yet clear how GLP-1r agonists cause weight loss, the fact that they do challenges the current model of the interaction of satiation factors with overall energy homeostasis.

Glicentin, GLP-2, oxyntomodulin, and glucagon

Other peptides derived from the processing of proglucagon include glicentin, GLP-2, and oxyntomodulin, as well as glucagon itself (39). Glicentin inhibits gastric acid secretion (74), but at least in rats, does not affect food intake (75). In contrast, oxyntomodulin, a C-terminally extended congener of glucagon, does reduce food intake in animals when given centrally or peripherally (75, 76). Although a unique receptor for oxyntomodulin has yet to be identified, oxyntomodulin may exert its anorectic effect through the GLP-1r because subthreshold doses of the GLP-1r antagonist, exendin (9–39), block both GLP-1 and oxyntomodulin-induced reductions in food intake (75). Oxyntomodulin is thought to cross the blood-brain barrier and stimulate neurons in the arcuate nucleus (ARC) that express GLP-1r.
and control energy homeostasis (77, 78). Long-term treatment with oxyntomodulin causes a persistent decrease in food intake and attenuated weight gain in rats (79). Interestingly, weight loss in animals given oxyntomodulin chronically is greater than what would be anticipated from reduced caloric intake (78), suggesting additional effects on energy expenditure.

Short-term treatment with iv oxyntomodulin decreases hunger, reduces consumption of an ad libitum meal, and has an anorectic action that persists for 12 h after cessation of treatment in lean humans (80). Moreover, in obese subjects randomized to injections of oxyntomodulin or placebo before each meal for 4 wk, there was a significant loss of weight associated with active treatment. Oxyntomodulin caused an approximately 0.5 kg/wk reduction in body weight and was generally well tolerated. These findings suggest that at least two proglucagon products may have a role in the regulation of food intake. Distinguishing between the effects of GLP-1 and oxyntomodulin, in particular the relative in vivo actions on the GLP-1r, is an important next step in applying these compounds to clinical medicine.

GLP-2 acts through a specific GLP-2 receptor to stimulate intestinal mucosal growth and has become the focus of research on short-bowel syndrome (81, 82). GLP-2 and GLP-1 have nearly 50% sequence homology and are secreted in parallel from perfused ileal preparations (83). Intracranial administration of GLP-2 reduces food intake in rats, and the effect can be blocked with a specific GLP-1r antagonist (84). More recent studies in humans found no effect of iv GLP-2 on food intake (85).

Glucagon is the most widely studied hormone cleaved from preproglucagon (39). It is secreted from both pancreatic A cells and probably also in small amounts from the distal intestine. The best known action of glucagon is to increase hepatic glucose production by stimulating glycogenolysis and gluconeogenesis. Glucagon also reduces meal size when administered systemically (86, 87), but not centrally (88), the signal being detected in the liver and relayed to the brain (89). A role for glucagon in the normal control of meal size was demonstrated by the observation that blocking endogenous glucagon action in rats increases food intake (90, 91). There is little convincing evidence that glucagon plays a role in food intake in healthy humans.

**Peptide tyrosine-tyrosine (PYY)**

PYY is a member of a family of homologous peptides that also includes pancreatic polypeptide and neuropeptide-Y (NPY). Like proglucagon-derived peptides, PYY is synthesized and secreted by L cells in the distal ileum and colon (92). PYY is secreted as PYY (1–36) and is metabolized to PYY (3–36) by DPP-IV (93, 94). Receptors that mediate the effects of PYY, including reduction of food intake, belong to the NPY receptor family and include Y1, Y2, Y4, and Y5 (95). However, PYY (3–36) is a highly selective agonist activity for the Y2 receptor, and it also reduces food intake in humans and animals (96, 97). Like GLP-1, PYY has been implicated in GI motility and is considered a major component of the ileal brake (98, 99). Secretion of PYY is stimulated by food intake (100) and also by the presence of nutrients within the ileum itself (101); lipid seems to be a particularly effective stimulus. Similar to the case with GLP-1, it is not clear whether PYY release requires direct nutrient contact with L cells, or if neurohormonal signals originating from the more proximal GI tract mediate the response. There is evidence that PYY influences food intake through its interaction with Y2 receptors in the ARC because it freely crosses the blood-brain barrier (102) and because systemic PYY (3–36) is ineffective in reducing food intake in the Y2-deficient mouse (103).

Studies in humans have demonstrated that PYY signaling reduces food intake and that abnormalities in this system are present in obese subjects. PYY secretion is proportional to the caloric content of meals, with larger meals eliciting a significantly larger response (104, 105). Fasting and postprandial levels of PYY are lower in obese adults compared with lean controls (105, 106). The attenuated rise in PYY after eating has also been observed in obese adolescents (107). Infusion of PYY (3–36) into lean and obese humans reduced food consumption measured during test meals (104–106), although there remains some question as to whether this effect of PYY (3–36) is pharmacological or occurs at circulating levels seen after eating. Obese subjects did not differ in their sensitivity to PYY, and there was no difference in the relative PYY (1–36) and PYY (3–36) levels after exogenous administration. Taken together, these findings suggest that abnormal PYY production, rather than anorectic action of metabolism, could contribute to obesity.

Interestingly, there is evidence that genetic variations in the PYY and Y2 sequences are associated with body weight. A common gene polymorphism in the Y2 receptor has been associated with a reduced likelihood of obesity in a cohort study of men with a broad range of BMI (108). Additionally, in a survey of lean and very obese men, a polymorphism in the PYY allele was found to segregate with increased body weight; this genetic variant of PYY was also found to have reduced binding to its receptor and an attenuated anorectic effect in mice (109). In total, the data collected in human studies support a role for PYY in the regulation of food intake and build the strongest case for any of the satiation factors in the pathogenesis of obesity.

**Apolipoprotein A-IV**

Apolipoprotein A-IV (apo A-IV) is synthesized by intestinal mucosal cells during the packaging of digested lipids into chylomicrons that subsequently enter the blood via the lymphatic system (110). Apo A-IV is also synthesized in the ARC (111). Systemic or central administration of apo A-IV reduces food intake and body weight of rats (112), and administration of apo A-IV antibodies increases food intake (113). Apo A-IV appears to work by interacting with the CCK signal (114). Because both intestinal and hypothalamic apo A-IV are regulated by absorption of lipid but not carbohydrate (115), this peptide may be an important link between short- and long-term regulators of body fat (see review by Tso and Liu in Ref. 116).

**Enterostatin**

A second digestion-related peptide, enterostatin, is also closely tied to intestinal processing of lipid. The exocrine pancreas secretes lipase and colipase to aid in the digestion of fat, and enterostatin, a pentapeptide, is cleaved from colipase in the intestinal lumen and enters the circulation. Administration of exogenous enterostatin either systemically (117, 118) or directly
into the brain (119) reduces food intake, and, when rats are given a choice of foods, the reduction is specific for fats; that is, enterostatin does not decrease the intake of carbohydrate or protein (120). Therefore, two 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. There are no data from human studies to confirm the findings with apo A-IV and enterostatin on food intake.

**Bombesin-family peptides**

Members of the bombesin family of peptides including bombesin itself (an amphibian peptide) and its mammalian analogs, gastrin-releasing peptide (GRP) and neureomedin B (NMB), reduce food intake when administered systemically in humans and animals or into the CNS of animals (121–123). Consistent with the possibility that these peptides act endogenously to reduce food intake, mice deficient for the GRP receptor eat significantly larger meals and develop late-onset obesity (124). Whereas most satiation factors act by reducing the size of an ongoing meal (4), bombesin peptides are an interesting exception in that when they are administered between meals, they increase the amount of time until the subsequent meal begins; *i.e.*, they increase satiety as well as satiation (125, 126).

Both bombesin and GRP reduce food intake when infused into human subjects (127, 128). Antagonism of endogenous bombesin receptors has demonstrable effects on gastric, intestinal, and gallbladder function but has not been studied with regard to food intake (129, 130). Therefore the case for GRP as a physiological mediator of satiation in humans is not as strong as for CCK.

**Amylin**

Amylin (also called islet amyloid polypeptide) is a peptide hormone secreted by pancreatic B cells in tandem with insulin secretion, which inhibits gastric emptying and gastric acid secretion, lowers glucagon concentrations, and reduces food intake (131). Amylin causes a dose-dependent reduction of meal size when administered systemically or directly into the brain (132–136), and antagonism of amylin action in the CNS causes increased food intake and body weight (137). Consistent with this, targeted deletion of the amylin gene causes increased body weight in mice.

Amylin signals through the calcitonin receptor when it has been modified by receptor activity modifying proteins (138, 139), and in contrast to many satiation peptides that reduce food intake by stimulating the visceral afferent nerves, amylin seems to act as a hormone, directly stimulating neurons in the area postrema in the hindbrain (133, 140). In fact, the anorectic action of amylin shares features with both satiation signals (phasic, meal-induced secretion) and adiposity signals (chronic interruption of action in rodents causes increased body fatness). Amylin seems to interact with both types of regulation in that the ability of amylin to reduce meal size is augmented when brain insulin action is elevated (141) and the effects of CCK and bombesin are muted in the absence of amylin signaling (142).

Amylin has been developed as a therapeutic, with the synthetic analog pramlintide now available for the treatment of type 1 and type 2 diabetes and clinical trials under way to determine the efficacy in treating obesity. In diabetic patients treated with pramlintide for 1 yr, weight loss averaged approximately 2 kg relative to placebo-treated controls (143, 144). Similar to treatment with the GLP-1r agonist exendin-4, pramlintide presents supraphysiological levels of amylin-like activity to patients, and the primary side effect is nausea. Nonetheless, the clinical experience with pramlintide supports the idea that chronic activity of a satiating compound can cause weight loss.

**Ghrelin**

Ghrelin, a product of specific endocrine cells in the stomach and duodenum, actually stimulates food intake and is the most potent known circulating orexigen (145). Ghrelin is secreted from the fundic region of the stomach and has been identified as the endogenous ligand for the GH secretagogue receptor. Fasting increases plasma ghrelin (146), and exogenous ghrelin increases food intake when administered peripherally or centrally (147–149). Ghrelin has also been linked to the anticipatory aspects of meal ingestion because levels peak shortly before scheduled meals in humans and rats (150) and fall shortly after meals end. Moreover, elevated ghrelin has been linked to the hyperphagia and obesity of individuals with the Prader-Willi syndrome (151). Ghrelin is also unique among the GI signals in that its message appears to be conveyed directly to receptors in the hypothalamus (152–155), although, as is the case for CCK, GLP-1, and other GI signals, there are ghrelin receptors on vagal sensory nerves (156) but they do not appear to signal satiation (157).

**Satiation signals: summary of general principles**

Satiation appears to be a complex phenomenon, mediated by a number of GI peptides. Although it is clear that the different satiation factors respond to specific nutrient stimuli (*e.g.*, CCK to protein and fat, GLP-1 to carbohydrate and fat, PYY primarily to fat, and so on), it has not been proven that mixed meals of differing macronutrient content elicit the release of distinct cocktails of GI hormones. However, given the wide range of specific factors that seem to mediate satiation, it is logical to presume that this process is subject to highly refined regulation. Especially important is the modulation of the action of satiation by factors such as leptin and insulin that are responsive to body adiposity. This interaction is the critical site of endocrine regulation of eating and energy homeostasis.

A key feature of the system regulating food intake is that most if not all of the peptides that are made in the GI tract and influence satiation are also synthesized in the brain. This includes CCK, GLP-1, GLP-2, oxyntomodulin, apo A-IV, GRP, NMB, PYY, and ghrelin. Exceptions are the pancreatic hormones that influence energy homeostasis (*i.e.*, insulin, glucagon, and amylin) and the adipose tissue/stomach hormone leptin; and each of these latter hormones has long-term effects on body fat as well. The fact that so many peripheral signals that influence food intake 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, GLP-1, apo A-IV, GRP, NMB, PYY, and ghrelin. Interestingly, it is also generally true 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 leptin, insulin, and amylin, but not glucagon.

It is worth contemplating why there is such a large imbalance among GI hormones that suppress and stimulate food intake; i.e., whereas numerous peptides secreted from the stomach and intestines decrease food intake, only one known factor, ghrelin, increases it. One possibility relates to the phenomenon of satiation itself and the benefits of meal termination. Meals end 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 their normal caloric load (158, 159). It has therefore been argued that a primary function of satiation signals is to prevent the consumption of too many calories at one time, lest the influx of nutrients and substrates overwhelm the capacity of the animal to maintain homeostasis (5, 160). That is, an important role of the GI tract is to analyze and respond to the incoming macronutrients while a meal is being eaten, helping to preempt excessive challenges to biochemical homeostasis. A corollary to this role for satiation signals is that adequate food intake does not require much specific stimulation, only the absence of inhibitory signals for food intake combined with the presence of food. Until recently there was some question as to whether manipulation of meal size by factors activating the satiation system could have therapeutic efficacy for weight reduction. One possibility was that because the effects of satiation peptides are dependent on body adiposity, their action would become muted as food intake decreased due to homeostatic regulation of body energy stores. Evidence for this was demonstrated for the satiating action of CCK in genetically obese Zucker rats (161, 162), but not for rats rendered obese by lesions of the ventromedial hypothalamus (163). Furthermore, rats genetically prone to becoming obese when fed a high-fat diet (diet-induced obesity rats) are actually more sensitive to the satiating action of CCK both before and after becoming obese (164). Some strains of genetically obese mice are comparably as sensitive as lean controls (165), and CCK works well in obese humans when administered iv (166). Hence, there is no general principle with regard to sensitivity in obesity, at least with regard to CCK. There is evidence that the satiating action of GLP-1 is leptin-dependent (167). All of these observations were made with animals having relatively free access to their diets so that they could vary their meal patterns in the service of maintaining body fat; i.e., when individuals are constrained to eating only small meals, they compensate by eating more often, thereby maintaining daily caloric intake and body weight. This has been observed when CCK is administered before every meal in experimental animals; animals receiving this treatment eat smaller and more frequent meals while keeping body weight constant (33, 168). In contrast, if animals are constrained to eating only three meals a day and receive a satiating peptide at each mealtime, they cannot compensate and consequently lose weight (169). The advent of long-acting formulations of GLP-1 and amylin, peptides that seem to have a role in satiation (170, 171), has resulted in weight loss (172, 173). However, at present it is not clear that the chronic effects of GLP-1 and amylin receptor agonists are entirely due to continued hypophagia as opposed to other, nonbehavioral actions of the compounds. Understanding how a chronic pharmacological stimulus to the satiation system lowers body weight is important for refining the models for normal energy homeostasis.

Adiposity Signals

Insulin from the pancreatic B cells and leptin from white adipocytes (as well as the stomach and other tissues) are each secreted in direct proportion to body fat. Both hormones are transported through the blood-brain barrier (174, 175) and gain access to neurons in the hypothalamus and elsewhere in the brain to influence energy homeostasis. Hence, neurons sensitive to insulin and/or leptin receive a signal directly proportional to the amount of fat in the body. Consistent with this, if exogenous insulin or leptin is added locally into the brain, the individual responds as if excess fat exists in the body; i.e., food intake is reduced and body weight is lost. Analogously, if either the leptin or the insulin signal is reduced locally in the brain, the individual responds as if insufficient fat is present in the body, more food is eaten, and the individual gains weight. There are many reviews of these phenomena (1, 2, 87, 176–178).

An important distinction is that whereas satiation signals primarily influence how many calories are eaten during individual meals, adiposity signals are more directly related to how much fat the body carries and maintains. Developing novel compounds that interact directly with the normal detection of and response to adiposity signals would therefore seem a more promising therapeutic approach for obesity. A key question therefore is whether agonists for the leptin and/or insulin receptor would be viable targets for the pharmaceutical industry. One obstacle is that to be effective, any compound would have to gain access to key receptors in the brain, yet any such compound would most likely have to be administered systemically. Administering insulin systemically elicits hypoglycemia and other side effects, and hypoglycemia per se increases food intake (179–181), thus working against the therapeutic intent. Systemically administered insulin does result in reduced food intake when plasma glucose is prevented from decreasing in animal models (182, 183), but this would be difficult to achieve therapeutically. Alternatively, there are reports that some formulations of nasally administered insulin elicit reduced food intake and body weight in humans without altering plasma glucose (184, 185).

Leptin does not have the same counterproductive systemic effects as insulin, and in fact improves insulin sensitivity and circulating lipoprotein concentrations in subjects with metabolic abnormalities associated with anti-HIV treatment (186). Moreover, chronic leptin treatment of patients with generalized lipodystrophy causes significant improvements of insulin resistance, hypertriglyceridemia, hepatic steatosis, and glucose metabolism (187), responses found across the spectrum of lipodystrophies.
However, the results of clinical trials using leptin in healthy obese subjects have been variable, with significant weight loss, but not of a remarkable magnitude, and some bothersome side effects related to peptide administration.

Insulin and leptin resistance characterize the obese state, meaning that more of each hormone is required to achieve a particular physiological effect than occurs in lean individuals. Individuals with diabetes cannot achieve a maximum insulin response because of defects in insulin secretion and insulin action. The insulin and leptin resistance that characterizes peripheral tissues in obesity is also manifested in the brain. For one thing, the transport of both hormones from the blood to the brain is compromised in obesity such that less signal reaches critical neurons (188–190), and the ability of those neurons to respond is also compromised. When insulin is administered locally into the brain near the hypothalamus, both genetically obese (191) and dietary obese individuals (192) have a reduced or absent reduction of food intake, and this is the case for leptin as well (193). Hence, an inability on the part of the brain to respond to signals indicating that there is excess fat in the body may be a contributing and/or confounding factor in obesity. An insulin mimetic that interacts with the insulin receptor and is efficacious when given orally or directly into the brain has been reported to reduce food intake and body weight in obese rodents (194, 195), but it evidently has problematic side effects.

**Central Integrating Circuits**

Although receptors for insulin and leptin are found in several discrete areas throughout the brain, many that are especially important for controlling energy homeostasis are localized in the ARC of the hypothalamus (Fig. 1). The ARC is ideally suited as a receptor site for body adiposity as well as for integration of diverse hormonal and neural signals because there is evidence that blood-borne molecules have relatively greater access to receptors there than to other brain areas, and this is thought to be due in part to a relatively leaky blood-brain barrier in the ARC (196, 197). Two categories of ARC neurons are particularly important. One synthesizes the prepropeptide, proopiomelanocortin (POMC), and in the ARC POMC is cleaved to α-melanocyte-stimulating hormone (αMSH) as a neurotransmitter. αMSH acts at melanocortin 3 and melanocortin 4 receptors (MC3R and MC4R) on neurons in other hypothalamic areas and elsewhere in the brain to reduce food intake, and synthetic agonists for MC3R/MC4R are available that cause hypophagia and weight loss in experimental animals (see reviews in Refs. 1, 2, 196, and 198–202). The catabolic action of both leptin and insulin relies upon αMSH signaling because administration of antagonists to MC3R/MC4R blocks each of their actions in the brain (203, 204).

The second group of ARC neurons synthesizes and secretes two neuropeptides important in energy homeostasis, and their axons project to many of the same brain areas as POMC neurons. Agouti-related peptide (AgRP) is an antagonist at MC3R and MC4R (199) such that one action of these neurons is to counter the activity of POMC neurons. NPY acts at Y receptors to stimulate food intake (205–207). When either AgRP or NPY is administered chronically into the brain, body weight increases (202, 208–211). In fact, when a single dose of AgRP is administered into the brain near the ARC, food intake is increased for 1 wk or more (212, 213). Insulin and leptin each have a net effect to suppress the activity of NPY/AgRP neurons in the ARC.

The POMC and NPY/AgRP neurons in the ARC share many important features. Each is the origin of tracts projecting to other hypothalamic and brain areas, the two tracts often occurring in parallel. The POMC-originating tract has an overall catabolic effect such that when it is more active food intake is reduced, energy expenditure is increased, and if prolonged, body fat is lost. Conversely, the NPY/AgRP-originating tract is anabolic, with heightened activity causing more food to be ingested and body fat to increase. Under normal conditions, both circuits are active such that a change of input that is either stimulatory or inhibitory to either type of neuron elicits rapid changes of many energetic parameters. In the acute situation, both food intake and plasma glucose are altered because the ARC influences circuits projecting to behavioral sites as well as autonomic circuits influencing hepatic glucose secretion and pancreatic insulin secretion (214–216).

Another important aspect of the area including the ARC and nearby hypothalamic nuclei is that receptors for many of the satiety signals discussed above are expressed there; i.e. circulating ghrelin is thought to interact directly with ARC neurons (152), which are also directly or indirectly sensitive to changes of CCK, GLP-1, NMB, and apo A-IV. Because most of these peptides are made within the brain, the origin of molecules altering ARC activity may not be directly from the plasma as occurs with insulin, leptin, and ghrelin. Numerous circuits from the hindbrain satiation area and elsewhere in the brain project to the region of the ARC (25, 27, 217). Finally, ARC neurons are also sensitive to local levels of energy-rich nutrients, including glucose (218), some long-chain fatty acids [e.g. oleic acid (219, 220)], and some amino acids [e.g. leucine (221)].

Thus, the ARC is situated to be sensitive to a wide array of signals important in energy regulation (216, 222–224). It is directly sensitive to hormones whose secretion is proportional to body fat (insulin and leptin); it receives information on ongoing meals either directly or indirectly; and it is sensitive to local levels of nutrients. Importantly, numerous neuronal circuits interconnect the ARC and nearby hypothalamic areas with the nucleus of the solitary tract, enabling the hypothalamic homeostatic network to be constantly aware of ongoing GI activity while at the same time influencing brain stem autonomic areas projecting to the GI tract, liver, pancreas, and other tissues (25, 27, 225–227). The ARC can therefore be considered as a key afferent as well as efferent area for the regulation of energy homeostasis.

Although ARC neurons project throughout the brain, two nearby target areas are thought to be especially important. The paraventricular nuclei (PVN) express both MC3R/MC4R and various Y receptors, and PVN neurons in turn synthesize and secrete neuropeptides that have a net catabolic action, including CRH and oxytocin. Administration of exogenous CRH (228) or oxytocin (229) into the brain reduces food intake. Hence, a catabolic circuit exists in which an increase of body fat is associated...
with increased insulin and leptin, increased αMSH, and decreased NPY and AgRP activity, and consequently increased activity of CRH, oxytocin, and other catabolic signals; all of these lead in turn to reduced food intake and increased energy expenditure.

The lateral hypothalamic area (LHA) has a contrasting profile from the PVN (230). It also receives direct inputs from the ARC, and it contains neurons that synthesize and secrete anabolic peptides, including melanin-concentrating hormone and the orexins. Administration of melanin-concentrating hormone (231, 232) or orexin agonists (233) increases food intake and body weight gain. The architecture and functioning of these opposing hypothalamic circuits therefore enables rapid and fine-tuned control over energy homeostasis because the brain can simultaneously turn up one system (e.g. catabolic or anabolic) while turning down the other.

Integration of Satiation and Adiposity Signals

Total food intake each day is the sum of the intake in individual meals (including snacks). As discussed above, the time that meals are initiated is often under the control of nonhomeostatic influences (4, 5, 160, 234). Hence, whatever regulatory control exists for body weight must be exerted on how much is eaten in individual meals, and meal termination is consequently under the influence of satiation signals. The efficacy of satiation signals to terminate a meal varies with the amount of fat in the body as signaled to the brain by leptin and insulin. When an individual has been food restricted (or been on a diet) and loses weight, leptin and insulin secretion both decline, and a reduced adiposity signal reaches the ARC. This in turn lowers sensitivity to satiation signals such as CCK, and the consequence is that more food is eaten during meals before satiation or feeling full occurs. Conversely, individuals who have overeaten and gained weight have elevated levels of adiposity signals and enhanced sensitivity to satiation signals, reducing the trajectory of weight gain or even promoting weight loss. When low doses of leptin or insulin are infused directly into the brain near the ARC, they greatly enhance the ability of satiation signals to reduce food intake [e.g. much less CCK or other adiposity signals is required to terminate a meal (235–241)], and when the adiposity signal in the brain is reduced, satiation signals are less efficacious (242).

Conclusion

The brain receives and integrates diverse information pertinent to the maintenance of energy homeostasis. Adiposity signals such as insulin and leptin act in the arcuate nuclei to provide a background tone, and this tone in turn determines the sensitivity of the brain to satiation signals influencing how much food is eaten at any one time. It is important to recognize that this “homeostatic” mechanism provides at most a background influence, and that it only subtly influences intake during any given meal. This is because social factors, palatability, habits, the presence of predators, stress, and many other factors are also always at work, influencing not only when meals occur but how much food is consumed as well. Only when extraneous factors are tightly controlled in laboratory animal experiments, or else when ingestion is precisely monitored and quantified over periods of days or weeks in free-feeding humans, do the effects of these homeostatic signals become apparent.

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