Signals That Regulate Food Intake and Energy Homeostasis

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Feeding behavior is critical for survival. In addition to providing all of the body's macronutrients (carbohydrates, lipids, and proteins) and most micronutrients (minerals and vitamins), feeding behavior is a fundamental aspect of energy homeostasis, the process by which body fuel stored in the form of adipose tissue is held constant over long intervals. For this process to occur, the amount of energy consumed must match precisely the amount of energy expended. This review focuses on the molecular signals that modulate food intake while integrating the body's immediate and long-term energy needs.

For the past 50 years, two types of model have dominated the study of food intake. The conceptually simpler "depletion-repletion" models propose that some parameter of immediately available energy be constantly monitored, with declining amounts triggering meal onset. Thus, a meal is initiated when available energy (for example, blood glucose or lipid availability or total energy derived from these fuels) falls to a threshold value and is terminated when substrate levels are sufficiently replenished. In principle, these models can account for both meal onset and meal termination. A well-known example is Mayer's glucostatic hypothesis (*1*), which postulates that small declines in glucose concentrations or utilization trigger meal initiation. Both the liver (*2*) and the brain (*1, 3*) have been hypothesized to monitor and respond to changes of immediately available energy in the control of food intake. However, although key parameters related to energy depletion and repletion correlate well with energy intake, they correlate poorly with energy expenditure. Depletion-repletion models, therefore, do not explain the matching of energy intake with expenditure that results in the long-term stability of fat stores.

The second type of model links food intake to the amount of stored energy (fat mass) in the body. This "lipostatic model," originally articulated by Kennedy (*4*), posits that signals proportional to the size of fat stores become integrated with other regulators of food intake. Thus, the onset of eating is not necessarily tied to immediate energy needs, nor is meal termination tied to the replenishment of depleted substrates. Rather, meal onset can occur for many reasons, including habits and learned associations, opportunity, social factors, and time of day (*5*). Similarly, meal termination can be influenced by many extrinsic factors, as well as by signals generated by the consumption of food (*5*), including signals generated in proportion to fat mass. Hence, animals consume meals when their lifestyle and the environment permit, and energy regulation occurs through modulation of the amount of food eaten at each meal to maintain energy stores. The continuous but variable needs of specific tissues are met by utilization of recently ingested calories during and immediately after meals and by drawing on stored energy at other times. The depletion of energy stored in the form of adipose tissue, therefore, increases food consumption, and this increase in consumption occurs primarily by increasing meal size. When food availability or energy stores are severely depleted, however, animals also initiate more frequent meals to survive (*5, 6*). A large and rapidly growing literature supports the hypothesis that food intake is controlled within a lipostatic system for energy homeostasis.

Regulation of Meal Number and Size

The average number of meals per day varies widely among and within animal species. When the daily light-dark cycle is fixed and when other constraints are controlled (for example, when there is ample food, low stress, and no predators or social competitors), species-specific meal patterns become apparent. Nocturnal laboratory rodents eat most food during the dark, with the largest meals occurring near the time that lights go on or off (*7*). Evidence of a weak but reliable association between meal size and the time lag before initiation of a subsequent meal suggests that factors determining meal onset are coupled to those terminating the meal (*8*). However, if confronted with periodic food-associated stimuli, variable food availability, changing social situations, or novel stimuli, animals readily modify their eating schedule while maintaining long-term energy homeostasis (*5*). Likewise, if physical constraints are placed on meal size or the number of available meals each day, animals readily modify their meal pattern so that sufficient calories are consumed to maintain fat stores (*5*). Thus, neither the timing nor the size of meals is fixed, and animals can accommodate a wide array of schedules to maintain energy balance. Because of this flexibility, controls must exist that determine meal size once eating has begun, to ensure that total intake is regulated. Consistent with this, a sizable literature has documented the existence of meal-generated signals, or "satiety factors," that accumulate during eating and ultimately contribute to meal termination (and hence determine meal size) (Fig. 1). The ability of these factors to impact meal size is modulated (at least indirectly) by the size of the fat mass.

Compelling evidence that satiety factors exist came in the early 1970s, when it was found that administration of the gut peptide cholecystokinin (CCK) to rats before the time of food availability caused a dose-dependent decrease in meal size (*9*). Since then, hundreds of animal and human studies have documented the generalizability of this phenomenon (*10*). Key conclusions from this literature are as follows.

1) CCK is but one of several peptides secreted from the gut during meals that, when administered exogenously, reduce meal size. Other potential satiety peptides include members of the bombesin family (bombesin, gastrin-releasing peptide, and neuromedin B) (*11*) and glucagon (*12*).

2) Blocking the action of endogenous satiety factors with specific antagonists or purified antibodies increases meal size (*10, 13*), implying that meal size is normally limited by these factors.

3) Satiety peptides combine with other signals to influence meal size. For example, when low-dose CCK-8 (a synthetic octapeptide of CCK) is coupled with mild gastric distension, meal size is reduced synergistically (*14*).

4) At doses that elicit modest reductions of meal size, satiety factors do not produce nausea or distress in animals (*10, 15*). When administered small doses of satiety factors, humans report feeling sated earlier in a meal without other untoward symptoms (*16*).

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5) Satiety peptides signal the brain through peripheral nerves (for example, vagal afferent fibers) as well as through receptors within the brain itself (*17*). This meal-related information is transmitted initially to the nucleus of the solitary tract, a brainstem area that integrates afferent signals arriving from the tongue (gustation) and gastrointestinal system (*18*). Afferent neuronal information then passes anteriorly through the brainstem to the hypothalamus and other forebrain areas. Importantly, CCK is effective at reducing meal size in chronic decerebrate animals in which all connections between the lower brainstem and the forebrain are severed (*19*). The necessary neuronal circuitry for this action of satiety factors is therefore contained within the lower brainstem.

6) Although satiety peptides can alter the size of individual meals, their repeated administration does not alter body weight. For example, when CCK-8 is automatically administered to rats at the start of each spontaneous meal, the size of each meal is reduced, but the animals compensate by initiating more meals and thereby maintain body weight (*20*). Hence, satiety factors can potently affect food intake over the course of individual meals but by themselves have limited influence on adiposity. It is this property that, when coupled with the success of energy homeostasis over long intervals, implies the existence of other signals, presumably proportional to the size of the adipose mass. Such long-term signals are not satiety signals per se but act over longer spans of time to suppress food intake by interacting with meal-related stimuli. It is through this interaction between long-term adiposity signals and meal-related satiety signals that the control of food intake is integrated into the homeostasis of fat stores.

Long-Term Regulation of Energy Balance

Energy homeostasis is accomplished through a highly integrated and redundant neurohumoral system that minimizes the impact of short-term fluctuations in energy balance on fat mass. Critical elements of this control system are hormones secreted in proportion to body adiposity, including leptin and insulin, and the central nervous system (CNS) targets upon which they act (*21*). Candidate CNS targets must exert potent unidirectional effects on energy balance in response to changes in body fat. They include those that stimulate food intake and promote weight gain (anabolic pathways), such as the hypothalamic neuropeptide Y (NPY) axis, and those that reduce food intake and promote weight loss (catabolic pathways), such as the hypothalamic melanocortin system. Hormones that are regulated by adipose tissue (insulin and leptin) inhibit central anabolic pathways and stimulate central catabolic pathways (Fig. 2).

Parabiosis studies performed by Coleman 30 years ago (*22*) suggested the existence of hormones that regulate food intake in inverse proportion to fat mass. Specifically, genetically obese *ob*/*ob* mice were hypothesized to lack such a hormone, and genetically obese *db*/*db* mice were proposed to be insensitive to the same hormone. These hypotheses were confirmed by the discoveries that the *ob* mutation resides in the gene encoding leptin (*23*), a hormone secreted from adipocytes, that the *db* mutation resides in the leptin receptor gene (*24*), and that leptin administration reverses obesity in *ob*/*ob* but not in *db*/*db* mice (*25*). Because direct administration of leptin into the CNS potently reduces food intake and because leptin receptors are expressed in hypothalamic areas important in the control of food intake (*26*), the brain is thought to be a primary target for leptin's anorexic effect. Leptin appears to be transported into the CNS by a saturable receptor-mediated

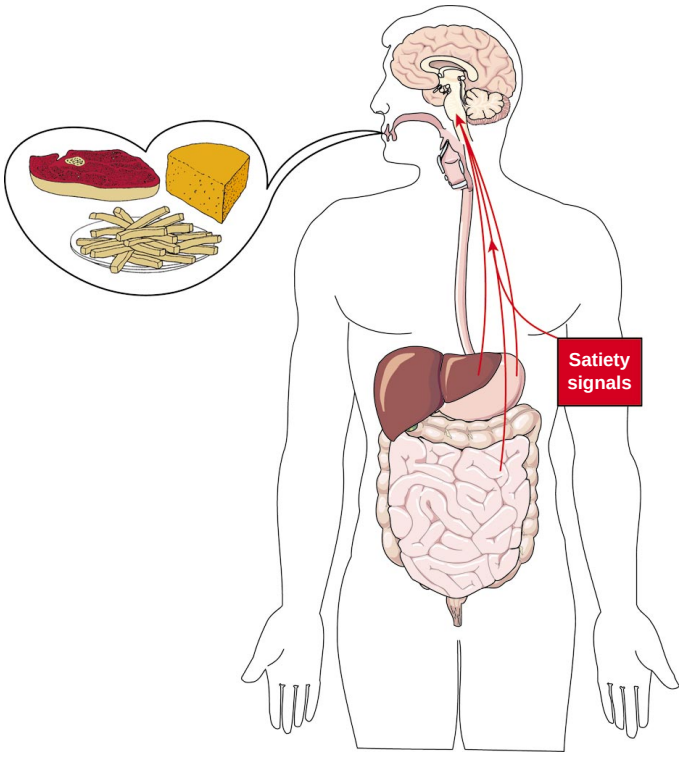

Fig. 1. The role of satiety signals in the control of food intake. Once eating has begun, food interacts with receptors on the tongue, the oropharynx, the stomach, and the duodenum, as well as in the liver and other organs. The detection, processing, and absorption of food generate "satiety" signals that provide negative feedback to the CNS, and these signals accumulate and interact to bring a meal to an end. The signals reach the brain through visceral afferent nerve fibers and through the blood.

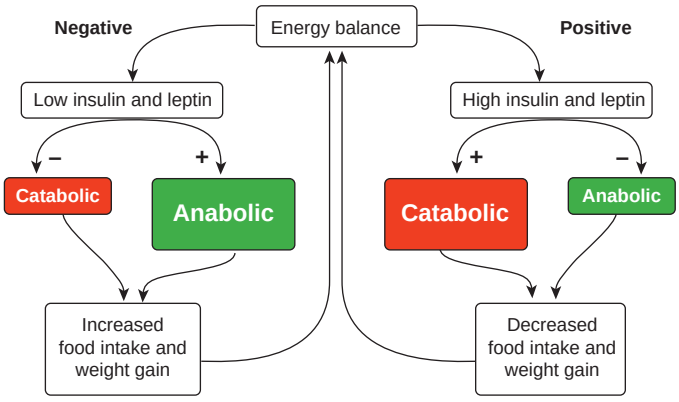

Fig. 2. The general circuitry underlying the regulation of body weight. Energy homeostasis is achieved when anabolic and catabolic influences are in balance over long intervals. The hormones leptin and insulin are secreted in direct proportion to the size of the adipose mass. During states of negative energy balance, the adipose mass contracts, and less leptin and insulin are secreted and reach the brain. As a result, anabolic pathways are disinhibited and catabolic pathways are suppressed, a condition that favors increased food intake and energy storage. Conversely, during states of positive energy balance, the adipose mass expands, leptin and insulin concentrations both increase, and the resulting output from the brain favors reduced food intake and a reduction of the size of the adipose mass. These key negative feedback circuits help ensure stability of the size of the adipose mass over time.

process, and the efficiency with which circulating leptin enters the brain is reduced when plasma concentrations are elevated (*27*). Leptin receptors in brain capillary endothelial cells (*28*) may mediate leptin's transport from blood to brain, and the observation that leptin concentrations in human cerebrospinal fluid correlate directly with plasma concentrations is consistent with its entry to the CNS from the plasma (*29*).

Leptin and insulin share many properties as adiposity signals. Although insulin is secreted from pancreatic beta cells rather than adipocytes, its circulating concentrations are proportional to adiposity (*30*). Insulin also enters the CNS by a receptor-mediated, saturable transport process across brain capillary endothelial cells (*31*), and insulin receptors are located in the same key hypothalamic areas as leptin receptors (*32*). Finally, like leptin, insulin reduces food intake and body weight in a dose-dependent manner when administered directly into the CNS, and neither hormone produces symptoms of malaise (*33*). The secretion of both leptin (*34*) and insulin (*30*) is influenced by the overall amount of fat stores as well as by short-term changes in energy balance (*35*), although insulin secretion is stimulated acutely in response to meals, whereas leptin secretion is not. The mechanisms governing leptin synthesis and secretion remain to be fully elucidated, but insulin appears to play a key role (*36*). In contrast to its immediate effect on circulating glucose, however, insulin's effect on circulating leptin concentrations is delayed for several hours (*37*).

One remarkable aspect of the catabolic response to leptin administration is that the weight loss appears to be due entirely to loss of fat (*38*). In fact, in some studies of normal, lean animals, continuous leptin administration can virtually eliminate detectable body adipose stores because of a relative increase of metabolic rate coupled with reduced energy intake (*38*). Under the influence of exogenous leptin, metabolic rate remains normal or elevated despite progressive weight loss (*39*). In contrast, metabolic rate falls sharply in animals with comparable weight loss due to caloric restriction, an effect associated with reduced activity of the sympathetic nervous system (SNS) (*40*). Because leptin increases SNS outflow (*41*), increased sympathetic activity may mediate its action on metabolic rate. Central insulin administration also reduces weight to a greater extent than can be accounted for by reduced caloric intake (*42*). Furthermore, when animals infused with insulin centrally are given a choice, they reduce their intake of dietary fat while sparing carbohydrate and protein reserves (*43*). Thus, leptin and insulin induce a spectrum of responses that leads to loss of body fat stores.

Except for leptin-deficient obese mice, most obese mammals have elevated plasma concentrations of leptin and insulin (*30, 34, 44*), and they appear to be resistant to leptin-induced anorexia. Thus, it remains to be determined whether human obesity can be successfully treated with continuous leptin administration. Systemic insulin administration is not a viable option for inducing weight loss because of its peripheral effects that enhance fat storage and reduce blood glucose concentrations. Moreover, at least some forms of obesity are associated with resistance to insulin's effects in the brain. Thus, genetically obese Zucker rats (*fa/fa*, with a mutation of the leptin receptor gene) do not reduce their food intake or body weight when given insulin intracerebroventricularly (*45*), suggesting that central leptin activity may be necessary for insulin signaling to occur. The nature of the interaction between leptin and insulin in the control of food intake, however, requires further study.

Central Effector Pathways

The hypothalamus contains multiple neuronal systems important in the regulation of energy homeostasis. For some systems (anabolic), stimulation results in a net increase of energy intake and storage, and for others (catabolic), stimulation results in a net decrease of energy intake and storage (Fig. 2). NPY is a neurotransmitter that is widely expressed throughout the brain. In the hypothalamus, a well-defined pathway that is implicated in NPY's effects on energy homeostasis originates in the arcuate nucleus (ARC). Axons project from NPY cell bodies in the ARC to the paraventricular nucleus (PVN) (*46*), a major integration site for inputs related to energy homeostasis. Central NPY administration promotes a state of positive energy balance and increased fat storage, with the most sensitive injection site being the PVN and adjacent perifornical area (*47*), where NPY receptors (both Y1 and Y5) are abundant (*48*). NPY injection into this brain area also reduces SNS outflow to brown adipose tissue (*49*), thereby lowering energy expenditure while simultaneously increasing the expression of enzymes involved in lipogenesis in white adipose tissue (*49*). Thus, central NPY administration increases energy intake, decreases energy expenditure, and increases lipogenesis. Repeated NPY administration into the PVN produces obesity within a matter of days (*47*).

The ARC-PVN NPY pathway is activated in response to signals associated with a decline in body fat stores. This response occurs during fasting as well as in uncontrolled insulin-deficiency diabetes mellitus, and it arises through increased NPY gene expression in ARC neurons and increased NPY release into the PVN (*50*). NPY activity in this pathway is increased in other conditions associated with weight loss, such as caloric restriction, lactation, and intense exercise (*51*), and this response is mediated, at least in part, by reduced negative feedback from insulin and leptin (*21*). NPY is overexpressed in the ARC of leptin-deficient *ob/ob* mice and leptin-resistant *db/db* mice (*52*), and this response is attenuated by leptin administration in *ob/ob* (but not *db/db*) mice (*53*). In normal rats, leptin administration also blunts the effect of fasting to increase hypothalamic NPY messenger RNA (mRNA) levels (*26*). Similarly, central insulin administration attenuates the increase in hypothalamic NPY mRNA levels that is associated with both fasting and insulin-deficiency diabetes (*54*). Combined with evidence that receptors for leptin and insulin are concentrated in the ARC (*26, 32*), these results suggest that the hypothalamic NPY system is normally inhibited by negative feedback provided by both insulin and leptin. Weight loss lowers the concentration of these hormones, an effect that in turn activates the NPY system, facilitating the recovery of lost weight. The finding that mice genetically deficient in NPY have apparently normal food intake and body weight (*55*) suggests that other systems can compensate for NPY's normal activities in energy homeostasis. The amelioration of the obesity and hyperglycemia in *ob/ob* mice deficient in NPY, however, demonstrates the potential contribution of unchecked NPY signaling in the syndrome that results from reduced leptin signaling (*55*).

Glucocorticoid (GC) hormones secreted by the adrenal cortex are also implicated in energy homeostasis by effects on NPY. Adrenalectomy attenuates the effect of fasting to increase both food intake and hypothalamic NPY gene expression, and these impairments are reversed by GC administration (*56*). Moreover, GC deficiency enhances the ability of insulin and leptin to promote anorexia and weight loss, and this effect is also reversed by GC administration (*57*). Taken together, these findings suggest that GCs are endogenous antagonists of leptin and insulin in the control of energy homeostasis.

NPY is not unique in its ability to increase food intake and body energy stores (Table 1). Central administration of other hypothalamic neuropeptides [melanin-concentrating hormone (MCH) and the recently described orexins A and B (also

identified as "hypocretins 1 and 2")] also stimulates food intake (58). As with NPY, expression of these peptides increases in response to fasting (58), suggesting that they may also play an important role in energy homeostasis.

Of particular interest among central catabolic systems are the melanocortins, peptides cleaved from the proopiomelanocortin (POMC) precursor polypeptide. In the mammalian forebrain, POMC gene expression is limited to ARC neurons that project to areas that participate in energy homeostasis [such as the PVN (59)]. These brain areas also express melanocortin (MC) receptors (specifically, MC3 and MC4 receptors), and agonists of these receptors elicit anorexia, whereas antagonists have the opposite effect (60). The endogenous melanocortin implicated most strongly in the control of food intake and body weight is α-melanocyte–stimulating hormone (α-MSH), which binds with high affinity to MC3 and MC4 receptors (61).

Because the CNS melanocortin system exerts effects opposite to those of NPY, it was anticipated that expression of POMC in the ARC would be regulated in a manner opposite to that of NPY, and indeed fasting has been found to reduce POMC mRNA levels in the ARC (62). This response is likely to be a consequence of reduced leptin signaling, as the level of POMC mRNA is also reduced in the ARC of *ob*/*ob* mice and leptin administration to these animals reverses this defect (62). Because leptin receptors are expressed on ARC POMC neurons (63), melanocortin neurons appear to be a target of leptin action. Consistent with this hypothesis, the ability of centrally administered leptin to lower food intake and to activate PVN neurons (as measured by induction of c-Fos expression) is blocked by pretreatment with a melanocortin receptor antagonist (64). Leptin's effect on energy homeostasis, therefore, appears to involve, at least in part, the activation of the hypothalamic melanocortin pathway. From this perspective, it is not surprising that impairment of melanocortin receptor signaling can cause obesity.

Evidence that melanocortins play a critical role in energy homeostasis derives from the observation that genetic deficiency of the MC4 receptor in mice results in hyperphagia and obesity (65). Ectopic production of agouti, an endogenous antagonist of MC receptors that is normally only expressed in skin, also produces an obesity phenotype. Production of agouti in the brain of "yellow obese," or "agouti," (A^y) mice antagonizes brain MC4 receptors and thereby results in obesity, whereas production of agouti in skin antagonizes melanocyte MC1 receptors and results in yellow coat color (65). The agouti-related protein (AGRP), another product of ARC neurons, shares sequence homology with agouti and is an antagonist of MC3 and MC4 receptors (66). Transgenic overexpression of AGRP also produces an obesity syndrome (66).

Another hypothalamic catabolic neuropeptide that contributes to energy homeostasis and that is regulated in part by leptin and insulin is corticotropin-releasing hormone (CRH), which is synthesized in PVN neurons (67). Central administration of CRH (or its recently described relative urocortin) reduces food intake and body weight, and endogenous CRH may be involved in stress and illness (68). Hypothalamic CRH gene expression is increased by leptin administration (26) and inhibited by GCs. Overproduction of CRH is implicated in the anorexia associated with adrenal insufficiency (21, 69), and reduced CRH signaling may contribute to the actions of GC hormones to promote weight gain and obesity (21, 69).

Leptin and insulin act, in part, by influencing the efficacy of meal-generated satiety peptides. For example, the effect of CCK to reduce meal size is potentiated by coadministration of either insulin or leptin (70). In this way, the size of the fat stores can influence daily feeding behavior by modulating sensitivity of the animal to signals generated by eating per se. An underweight individual who has reduced leptin and insulin concentrations is therefore less sensitive to single-meal satiety signals; hence, larger meals are consumed when conditions permit. Likewise, an animal that has recently overeaten and gained excess weight will be more sensi-

Table 1. Candidate signaling molecules involved in energy homeostasis in the CNS.

Catabolic	Anabolic
CRH*	NPY*
α-MSH*	AGRP*
CCK	MCH
Bombesin	orexins A and B (= hypocretins 1 and 2)
Somatostatin	galanin
Thyrotropin-releasing hormone	β-endorphin
Calcitonin-gene–related peptide	dynorphin
Neurotensin	norepinephrine
Glucagon-like peptide–1	growth hormone–releasing hormone
Serotonin	

*These molecules are particularly important in the regulation of adiposity.

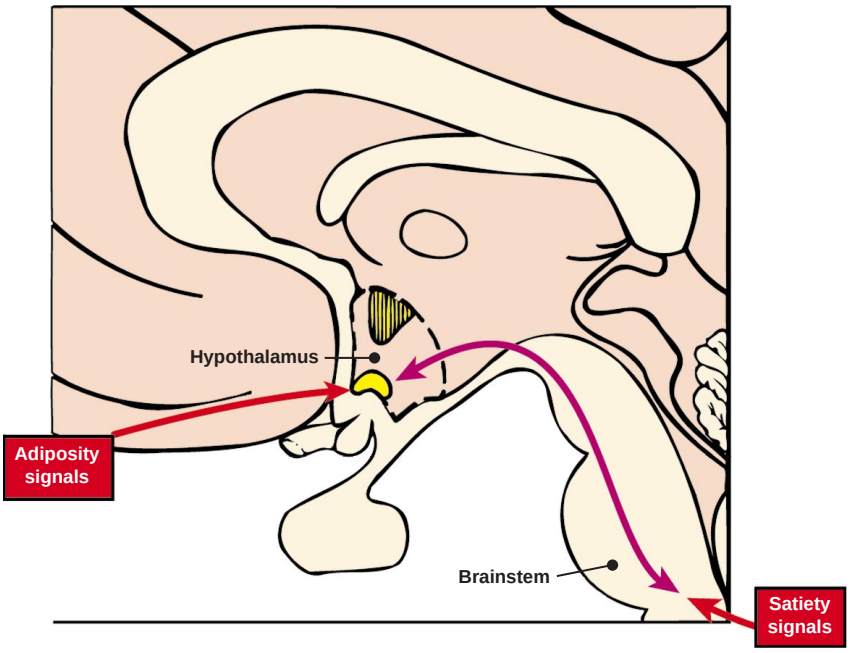

Fig. 3. Integration of feeding-related signals from adipose tissue, the gut, and the brain. The circulating adipose signals leptin and insulin penetrate the blood brain barrier and stimulate receptors on neurons in the hypothalamus. Satiety signals generated by ingested food enter the caudal brainstem (either as hormones that act locally on neurons within the brainstem itself or through visceral afferent signals originating in the mouth or gut), where they influence reflexes related to the acceptance or rejection of food. Satiety information is also relayed anteriorly to the hypothalamus, where it is integrated with cognitive information and adiposity signals. Increased activity of adiposity signals enhances the ability of satiety signals to terminate a meal. The integrated information is then relayed back to the brainstem to areas controlling food intake and energy expenditure.

tive to meal-generated signals and tend to eat smaller meals over time. Two points are noteworthy. First, the location of integration of adiposity and satiety signals is not known, nor is it clear how satiety signals interact with the hypothalamic anabolic and catabolic systems described above. The observation that decerebrate animals respond to satiety signals but do not regulate the size of their adipose mass (*19*) suggests that the forebrain is key to the integration process. This concept is compatible with the role of the hypothalamus as a major integration site for adiposity signals (Fig. 3). Second, the time constant with which adiposity signals influence food intake is much longer than the span of one or a few meals. The best estimates in humans and other mammals suggest that whereas social and other constraints constantly influence how much is eaten in individual meals, regulation of adiposity is integrated only over intervals of several days (*71*).

Summary

Like other homeostatic systems, weight regulation is notable for its highly integrated and redundant nature. It is therefore not surprising that multiple adiposity signals exist and that many CNS pathways participate in the response to these signals. The response to weight loss resulting from inadequate caloric intake is a case in point. Insulin and leptin concentrations decrease and GC concentrations increase, a combination that activates pathways that stimulate appetite and promote weight gain while simultaneously inhibiting pathways that have the opposite effect. This combined effect maximizes the homeostatic response to weight loss and, consequently, the efficiency with which depleted fuel stores are replenished. Although such a robust system for defending fat stores may have conferred a survival advantage during human evolution, it now poses a formidable challenge for the treatment of obesity. Individuals who suffer from a regulatory defect that results in the defense of an elevated amount of body fat appear to resist changes in energy stores with the vigor characteristic of lean individuals (*72*). Finding a "magic bullet" for the treatment of obesity may therefore be unrealistic. Rather, interventions directed at multiple targets in the energy homeostasis system might be necessary to achieve and maintain weight loss.

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Strategies and Potential Molecular Targets for Obesity Treatment

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Obesity is an increasingly prevalent and important health problem. Although treatment is available, the long-term maintenance of medically significant weight loss (5 to 10 percent of initial body weight) is rare. Since 1995 there has been an explosion of research focused on the regulation of energy balance and fat mass. Characterization of obesity-associated gene products has revealed new biochemical pathways and molecular targets for pharmacological intervention that will likely lead to new treatments. Ideally, these treatments will be viewed as adjuncts to behavioral and lifestyle changes aimed at maintenance of weight loss and improved health.

Obesity is an increasingly prevalent, costly, and important health problem throughout the world (*1, 2*). In the United States, the prevalence of obesity in adults is now 32%, and the prevalence in children has risen by 40% over the last 16 years. Similar trends are being seen worldwide (*1*).

Obesity is a particularly challenging medical condition to treat because of its complex etiology. Body weight represents the integration of many biological and environmental components. The environmental components (*3*) can be modulated through behavioral changes such as healthy eating and physical activity, whereas the biological components are much more difficult to address. Changes in body weight are resisted by very robust physiologic mechanisms that we are only beginning to understand (*4–6*). However, the recent explosion of research on the altered biochemical pathways caused by single gene mutations in animal models of obesity has dramatically expanded our knowledge base of these physiologic mechanisms (*6*). As a result, efforts to develop innovative anti-obesity drugs have intensified. Here, we discuss some of the potential drug targets that have emerged from this "new science" of obesity.

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Assessing the Efficacy of Obesity Treatments

Traditionally, the efficacy of a new obesity treatment is assessed by its effect on body weight. By this criterion, a treatment is considered successful if it (i) prevents further weight gain, (ii) induces a 5 to 10% weight loss from the initial body weight, and (iii) allows long-term maintenance of the weight loss once it is achieved (*1, 7*).

Recently, an alternative, medically based outcome measure for obesity treatment has been advocated by scientists and physicians (*7*). Rather than focusing primarily on body weight, body fat, or the body mass index (BMI = weight/height^2), this measure, called "metabolic fitness," tracks the metabolic health of obese individuals. Metabolic fitness is defined as the absence of biochemical risk factors associated with obesity, such as elevated fasting concentrations of cholesterol, triglycerides, glucose, or insulin; impaired glucose tolerance; or elevated blood pressure. In this school of thought, weight loss is viewed not as a goal but as a modality to improve health (*7*). Many studies have shown that during periods of weight loss there is a uniform improvement in the profile of risk factors (*1*). Interestingly, reductions in the biochemical risk factors may not always be dependent on weight loss. For example, insulin sensitivity and cholesterol levels can be improved by physical activity in the absence of weight loss (*1, 3, 8*). The hope is that by using metabolic fitness as a measure of success, health professionals can shift the patient's focus from unrealistic, culturally imposed goals (for example, dress size or belt size), to the more appropriate and achievable goal of better health (*7*).

Classes of Anti-Obesity Drugs

Anti-obesity drugs can be classified according to their primary mechanism of action on energy balance. When daily energy intake matches daily energy expenditure, body weight remains constant. If intake exceeds expenditure, then a state of positive energy balance is achieved and body weight will increase. Conversely, if energy expenditure exceeds intake, then a state of negative energy balance is achieved and body weight will decrease. The goal of all anti-obesity drugs is to induce and maintain a state of negative energy balance until the desired weight loss is achieved (*4, 5, 9–11*).

There are four general classes of anti-obesity drugs. (i) Inhibitors of energy (food) intake (or appetite suppressants) reduce hunger perception, increase the feeling of fullness, and reduce food intake by acting on brain mechanisms. As a result, these drugs facilitate compliance with caloric restriction. (ii) Inhibitors of fat absorption reduce energy intake through a peripheral, gastrointestinal mechanism of action and do not alter brain chemistry. (iii) Enhancers of energy expenditure act through peripheral mechanisms to increase thermogenesis without requiring planned increases in physical activity. (iv) Stimulators of fat mobilization act peripherally to reduce fat mass or decrease triglyceride synthesis or both without requiring planned increases in physical activity or decreases in food intake. Importantly, the beneficial actions of all four drug classes can be easily overcome by increased intake of food (especially calorically dense food items) or decreased voluntary physical activity.

The major drugs used to treat obesity are shown in Table 1. Currently, the only drugs approved for use are a small set of centrally acting appetite suppressants that reduce food intake by modulating the concentrations of monoamine neurotransmitters (serotonin and norepinephrine or norepinephrine alone) in the brain. This modulation can occur at the level of neurotransmitter release or re-uptake or both. The identifi-