Model for the regulation of energy balance and adiposity by the central nervous system[1–3]

Michael W Schwartz, Denis G Baskin, Karl J Kaiyala, and Stephen C Woods

ABSTRACT In 1995, we described a new model for adiposity regulation. Since then, data regarding the biology of body weight regulation has accumulated at a remarkable rate and has both modified and strengthened our understanding of this homeostatic system. In this review we integrate new information into a revised model for further understanding this important regulatory process. Our model of energy homeostasis proposes that long-term adiposity-related signals such as insulin and leptin influence the neuronal activity of central effector pathways that serve as controllers of energy balance. Am J Clin Nutr 1999;69:584–96.

KEY WORDS Body weight, adipose tissue, food intake, insulin, leptin, neuropeptide Y, glucocorticoids, obesity, energy balance, central nervous system, homeostasis, central effector pathways, arcuate nucleus, paraventricular nucleus, review

INTRODUCTION

In 1995, we described a new model for adiposity regulation in a supplement to the Journal (1). We proposed that discrete neuronal circuits exist within the brain that, when activated, exert potent, unidirectional effects on energy balance. We hypothesized that these central effector pathways transduce afferent input from adiposity-related hormonal signals into changes in feeding behavior and energy balance. Through this mechanism, the central nervous system (CNS) response to afferent signals that control the size of individual meals was proposed to be adjusted in proportion to changes in body adiposity, resulting in the long-term stability of fat stores. The present article integrates new information into a revised model for understanding this important regulatory process (**Figure 1**).

Over the course of a single day, the amount of energy ingested can be influenced by a nearly infinite number of variables. Despite this short-term variability in energy intake, body fuel stored in the form of adipose tissue remains relatively constant over time (2–4). These observations suggest the existence of a homeostatic mechanism whereby short-term mismatches in energy balance (ie, the difference between energy consumed and that expended) are compensated for over long time intervals. Much evidence supports this concept. For example, changes in body fat content induced by such diverse interventions as dieting (5, 6), behavior modification (3, 6), surgical removal of fat (7–9), or experimental overfeeding (10, 11) induce compensatory responses that gradually restore adiposity to baseline values. The limited success of energy-restricted diets as an approach to achieving long-term weight loss in the treatment of obesity (4–6) underscores the clinical importance of this regulatory system.

Food intake and energy expenditure are influenced over the short term by input from a wide variety of situational and meal-related factors. Within this broad category are physiologic signals, including neuronal information related to ongoing circadian rhythms, metabolic signals reflecting the rate of utilization of different fuels by brain and abdominal viscera, gastrointestinal signals resulting from gastric distention, and the release of peptides from the gastrointestinal tract in response to nutrient ingestion. Emotional factors and the palatability and nutrient content of available food are additional inputs that can exert strong, transient effects on the amount and type of food consumed from one meal to the next. Because short-term factors can arise unpredictably and can influence powerfully the size and frequency of meals, variability in daily patterns of energy intake is the rule. Moreover, because short-term, meal-related signals are not generated in proportion to energy requirements, daily food intake and energy expenditure are not closely correlated in humans (12).

The biological system that regulates body adiposity was hypothesized 46 y ago (13) to involve humoral signals generated in proportion to body fat stores that act in the brain to alter food intake and energy expenditure. Major candidates for such signals include the hormones insulin (14) and leptin (15), both of which are secreted in proportion to body adiposity and act in the brain to reduce food intake and promote weight loss. In contrast with short-term inputs, insulin and leptin exert effects in the CNS that are slow in onset and offset (eg, hours to days), with an effect

[1] From the Departments of Medicine, Biological Structure, and Psychology, University of Washington, Harborview Medical Center and the VA Puget Sound Health Care System, Seattle; and the Department of Psychiatry, University of Cincinnati.

[2] Supported by grants from the NIH (DK-12829, DK-52989, and NS-32273), the Diabetes Endocrinology Research Center and Clinical Nutrition Research Unit at the University of Washington, and the VA Merit Review Program.

[3] Address reprint requests to MW Schwartz, Department of Medicine, University of Washington and the VA Puget Sound Health Care System, 1660 South Columbian Way, Seattle, WA 98108. E-mail: mschwart@u.washington.edu.

Received March 19, 1998.

Accepted for publication August 13, 1998.

Am J Clin Nutr 1999;69:584–96. Printed in USA.

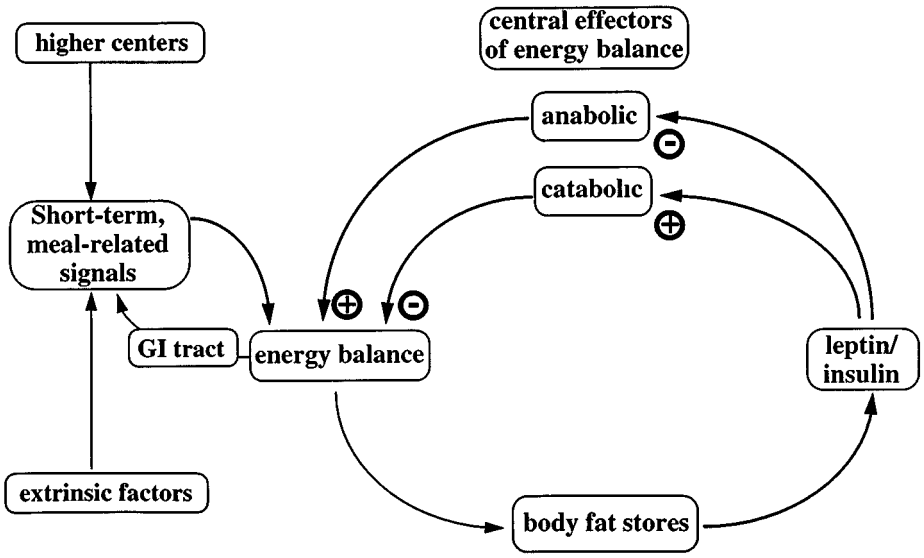

FIGURE 1. Model for the regulation of energy balance and adiposity. Neural systems termed central effectors of energy balance represent major controllers of food intake and autonomic outflow that affect the storage and mobilization of energy. Anabolic effector pathways promote feeding and suppress energy expenditure, whereas catabolic effector pathways have the opposite effect. Short-term, situational, and meal-related signals originate from various internal sources [eg, cholecystokinin secretion from the gastrointestinal (GI) tract], from the environment (eg, food-related cues), and from higher centers (eg, emotional and cognitive factors). Although short-term signals are major determinants of the size and timing of individual meals, their effect on fat stores is limited by the long-term regulation of energy homeostasis. This is because long-term, adiposity-related signals such as insulin and leptin regulate the output of the central effector pathways and modulate the central nervous system response to short-term signals in proportion to the level of fat stores. In this way, changes in energy balance that alter fat stores elicit compensatory responses in central effector pathways that preserve energy homeostasis.

that is sustained over long intervals. These hormones appear to regulate the activity of neuronal systems that strongly influence energy homeostasis, referred to here as central effector pathways. In this article, we advance the thesis that energy balance is achieved and maintained over long time intervals (eg, weeks to months) via the activation of key brain systems in response to a change in fat stores, triggered in part by changes in signaling by leptin and insulin (16).

CENTRAL EFFECTOR PATHWAYS FOR CONTROL OF ENERGY BALANCE

Many neuropeptides and monoamines synthesized and released along discrete neuronal pathways within the brain can modify food intake when administered to the CNS (**Table 1**). An increasing number of these have been implicated as endogenous signaling molecules, which play an important role in energy homeostasis. We propose that candidate central effector pathways must meet the following criteria: they strongly influence both energy intake and energy expenditure and their activity is regulated by adiposity-related signals.

Central effector pathways can be defined as either anabolic or catabolic, terms that reflect the overall effect on energy balance brought about through stimulation of the pathway. Elevated neuronal activity in anabolic pathways promotes a state of positive energy balance by stimulating the ingestion and storage of energy, whereas stimulation of catabolic pathways causes a net loss of energy from the body. Anabolic systems act primarily by increasing the drive for food intake, although they may also decrease energy expenditure, alter the peripheral metabolic environment to favor assimilation and storage of ingested energy, or both. In contrast, catabolic effector systems promote the mobilization of stored fat and cause weight loss by reducing food intake, increasing lipolysis and thermogenesis, or both. Available evidence suggests that the peripheral metabolic effects of central neuropeptides and monoamines are mediated by efferent autonomic activity. As a general rule, elevated sympathetic nervous system (SNS) outflow promotes catabolic effects and a decreased SNS outflow favors anabolic actions (17, 18), whereas the reverse applies to efferent activity of the parasympathetic nervous system (17, 19).

CANDIDATE ANABOLIC EFFECTOR SYSTEMS

Neuropeptide Y

Neuropeptide Y (NPY) is a member of the pancreatic polypeptide family that is synthesized in peripheral sympathetic neurons as well as in the brain. In the CNS, the actions of NPY on energy homeostasis are exerted largely within the hypothalamus. The primary hypothalamic site of NPY biosynthesis is the arcuate nucleus (20), a collection of neuronal cell bodies located adjacent to the floor of the third cerebral ventricle. Axons from these neurons project to several other hypothalamic nuclei, including the paraventricular nucleus, a key brain area mediating a potent effect of NPY to stimulate feeding (21). Daily injection of NPY into the hypothalamic paraventricular nucleus not only causes sustained hyperphagia and weight gain (20–22), but also has metabolic actions that favor fat deposition. These include increased lipoprotein lipase gene expression and enzyme activity

in white adipose tissue (23), enhanced lipogenesis in both liver and white adipose tissue, and increased secretion of insulin and glucocorticoids into the circulation (24). Because these metabolic effects of intracerebroventricular NPY administration are detected even when hyperphagia is prevented, they are not simply a consequence of increased energy intake. The ability of intracerebroventricular NPY to reduce SNS activity (18, 23) may account for these metabolic actions.

NPY also promotes weight gain by reducing SNS outflow to brown adipose tissue (BAT), a form of adipose tissue that is specialized for the purpose of heat production. BAT is richly supplied with SNS fibers and stimulation of these fibers elicits a thermogenic response via a process that requires a mitochondrial protein unique to BAT known as uncoupling protein 1 (UCP-1). After SNS activation of BAT, oxidation of fatty acids in mitochondria that contain UCP-1 yield energy in the form of heat rather than ATP generation. By reducing SNS outflow to BAT (18), NPY injection into the brain increases energy efficiency by suppressing this thermogenic mechanism (23).

A physiologic role for the hypothalamic NPY system in energy homeostasis is suggested by evidence that its production (within the arcuate nucleus) and release (into the paraventricular nucleus) are affected by changes in energy balance. Thus, conditions associated with weight loss, such as food deprivation (25–28) and uncontrolled insulin-deficient diabetes (29–33) increase production and release of NPY along the arcuate nucleus–paraventricular nucleus pathway, and this response may contribute to the hyperphagia common to both conditions. Activation of the hypothalamic NPY system in these conditions appears to involve decreased signaling by insulin and leptin, combined with increased glucocorticoid concentrations (26, 31, 34–36).

Genetic obesity resulting from defective leptin signaling appears to result in part from inappropriate activation of NPY-containing hypothalamic pathways. This conclusion is supported by the observation that hypothalamic NPY messenger RNA (mRNA) concentrations are elevated in fa/fa obese Zucker rats (37, 38), in ob/ob mice (39), and in db/db mice (40). Because obesity in these animals results from mutation of either the gene encoding the leptin receptor (in db/db mice and fa/fa rats) or leptin itself (in ob/ob mice), defective leptin signaling appears to activate the NPY system.

The finding that inhibition of NPY biosynthesis in the arcuate nucleus by direct application of antisense oligonucleotides is associated with reduced food intake (41) and a blunted hyperphagic response to fasting in rats (42) suggests that variations in endogenous NPY signaling contribute to the normal regulation of food intake. Similar conclusions have been drawn from studies in which hypothalamic NPY signaling was reduced by immunoneutralization (43, 44) or by intracerebroventricular infusion of antisense oligonucleotides directed to the Y_5 receptor (42), which is proposed to mediate the effects of NPY on food intake (45). However, mice with genetic NPY deficiency (due to targeted gene disruption or gene knockout) maintain relatively normal patterns of food intake and body weight gain (46); mice that lack Y_5 receptors paradoxically develop a mild, late onset form of obesity (47), as do mice lacking Y_1 receptors (48). Excessive weight gain in Y_1 receptor–deficient mice was attributed to reduced locomotor activity and occurred despite food intakes that were lower than those of controls (48). Although these findings do not support the hypothesis that NPY is required for maintenance of normal food intakes, mice lacking Y_1 receptors also have reduced food intakes in response to fasting. Y_1 receptor signaling, therefore, appears to be important for the hyperphagic response that facilitates the recovery of depleted fuel stores following food deprivation. In contrast, the effect of fasting to stimulate food intake is intact in mice lacking NPY (46). These conflicting results raise the possibility that genetic deficiency of a major CNS signaling system can result in a compensatory "rewiring" of neuronal circuits involved in energy homeostasis, and that the extent to which this occurs can vary with the nature of the mutation. Alternatively, CNS pathways that control food intake may be sufficiently redundant to compensate for the loss of even a major signaling system. This possibility agrees with a growing literature suggesting that neuronal systems additional to NPY play an important role in weight regulation.

TABLE 1
Some candidate signaling molecules used by central effector pathways involved in the hypothalamic control of energy balance[1]

	Effect on food intake	Effect on SNS activity
Catabolic		
Corticotropin-releasing hormone[2]	↓↓	↑↑
α-MSH[2]	↓	?
CART[2]	↓	?
Bombesin	↓	↑
Somatostatin	↓	?
Cholecystokinin	↓	↑
Thyrotropin-releasing hormone	↓	?
Calcitonin-gene–related peptide	↓	↑
Neurotensin	↓	↑
Serotonin	↓	↑
Anabolic		
Neuropeptide Y[3]	↑↑	↓↓
Melanin concentrating hormone[3]	↑	?
Agouti-related protein[3]	↑	?
Orexin A and B[3]	↑	?
Galanin	↑	?
β-Endorphin	↑	↓
Dynorphin	↑	?
Growth hormone–releasing hormone	↑	↓
Norepinephrine	↑	↓

[1] ↑, increase; ↓, decrease; ?, not established; double arrows indicate robust effects; SNS, sympathetic nervous system; MSH, α-melanocyte-stimulating hormone; CART, cocaine- and amphetamine-regulated transcript.
[2] Pathways that are stimulated by leptin.
[3] Pathways that are inhibited by leptin, activated by fasting, or both.

Melanin concentrating hormone and orexins

Melanin concentrating hormone (MCH) (49) and orexins A and B (50), also referred to as hypocretins 1 and 2 (51), are hypothalamic neuropeptides that share several features in common and are implicated in the stimulatory control of food intake. Both peptides are expressed exclusively in the dorsolateral hypothalamus and both have extensive projections to other brain areas (49, 50). Both peptides also stimulate food intake robustly after injection into brain ventricles, and expression of mRNA encoding these peptides increases in response to fasting, features in common with NPY. These results suggest that the hyperphagic response to conditions associated with weight loss involves the activation of multiple neuropeptide systems in the hypothala-

TABLE 2
Monogenic obesity syndromes involving leptin or melanocortin (MC) signaling systems in rodents[1]

Mutation	Species	Affected gene	Pathogenesis
Leptin and leptin receptor defects			
ob/ob	Mouse	Leptin	Leptin deficiency
db/db	Mouse	Leptin receptor	Leptin resistance
fa/fa	Rat	Leptin receptor	Leptin resistance
MC receptor defects			
A^y	Mouse	Agouti	Antagonism of MC-R
Transgenic agouti overexpression	Mouse	Agouti	Antagonism of MC-R
Transgenic AgRP overexpression	Mouse	AgRP	Antagonism of MC-R
MC4-R knockout	Mouse	MC4-R	MC resistance

[1] AgRP, agouti-related protein; A^y, yellow obese agouti.

mus. The mechanisms underlying the regulation of these MCH and orexin neurons, however, are unknown, and the possibility that both neuropeptides are expressed within the same neurons has yet to be explored. Although the hypothesis that these neurons are targets for the action of negative feedback from hormones such as leptin and insulin is attractive, the receptors for these hormones are not abundantly expressed in the dorsolateral hypothalamus compared with areas such as the arcuate nucleus (34, 52). Regulation of these neuronal systems by leptin or insulin, if it occurs, is likely to involve an indirect signaling pathway.

CATABOLIC CENTRAL EFFECTOR PATHWAYS

Melanocortins

The melanocortin signaling system in the brain is an important member of the family of catabolic central effector pathways proposed to transduce changes in CNS leptin signaling into changes in food intake and body weight. Melanocortins are a family of peptides, including α-melanocyte-stimulating hormone (α-MSH) and corticotropin, that are cleaved from the proopiomelanocortin precursor. In the mammalian forebrain, proopiomelanocortin is expressed solely by neurons of the arcuate nucleus, adjacent to NPY-producing cells. These neurons release α-MSH from axon terminals (53), where it can bind to and activate melanocortin receptors on postsynaptic membrane surfaces. Of the 5 melanocortin receptor subtypes identified to date, 2 are expressed primarily in the brain (MC3 and MC4 receptors) (54). The MC4 receptor is strongly implicated in energy homeostasis because genetic knockout of this receptor subtype causes hyperphagia and obesity in mice (55) (Table 2) and because intracerebroventricular administration of an MC4 receptor agonist causes anorexia, whereas antagonists of MC4 receptors stimulate feeding (56). These observations implicate the melanocortin system as a catabolic effector pathway that plays a key role in energy homeostasis.

Consistent with this hypothesis, leptin deficiency in ob/ob mice is associated with reduced proopiomelanocortin mRNA concentrations in the arcuate nucleus; leptin administration reverses this defect (57). Moreover, leptin receptor mRNA is colocalized with proopiomelanocortin mRNA in arcuate nucleus neurons (58), suggesting that these proopiomelanocortin neurons are targets for leptin action. The recent observation that the effect of a single dose of intracerebroventricular leptin to lower food intake and body weight is completely prevented by pretreatment with an MC4 receptor antagonist (59) supports the hypothesis that the arcuate nucleus proopiomelanocortin system is an important mediator of leptin action in the brain.

Agouti and agouti-related protein: endogenous melanocortin receptor antagonists

A unique feature of the melanocortin system is the presence of endogenous antagonists of melanocortin receptors. The first of these to be discovered is agouti, a protein synthesized in skin and hair follicles that is released in a paracrine manner to antagonize α-MSH at cutaneous MC1 receptors (60). This mechanism explains the lightening effect of agouti on coat color because melanin production in hair follicles is stimulated by the ability of circulating α-MSH to bind to and activate cutaneous MC1 receptors. Evidence that antagonism of CNS melanocortin receptors can cause obesity was first provided in the yellow obese or agouti (A^y) mouse, an autosomal dominant model of genetic obesity (**Table 2**). This condition results from a gene rearrangement that causes ubiquitous expression of agouti in tissues throughout the body, including the brain. Because agouti antagonizes MC4 receptors as well as MC1 receptors, this form of obesity appears to result from antagonism of melanocortin receptors in the brain, whereas the yellow coat color arises from antagonism of the melanocortin receptors in the hair follicle (60).

A second endogenous melanocortin receptor antagonist, known as agouti-related protein (AgRP), was identified recently based on sequence homology to the agouti gene (61). In contrast with agouti, the gene encoding AgRP is normally expressed in the CNS (61) and appears to function as an endogenous antagonist of CNS melanocortin receptors (62). Consistent with this hypothesis, AgRP antagonizes α-MSH at both MC3 and MC4 receptors, but not at MC1 receptors (62). Moreover, transgenic overexpression of AgRP in tissues throughout the body (by using a β-actin promoter) causes an obesity syndrome in mice that is virtually identical to that associated with overexpression of agouti, except that coat color is not affected in AgRP-transgenic mice (62), presumably because AgRP does not antagonize cutaneous MC1 receptors. In the brain of normal animals, mRNA encoding AgRP is expressed only in the arcuate nucleus (61) and AgRP mRNA is highly co-localized with NPY, but not with proopiomelanocortin mRNA in arcuate nucleus neurons (63). Like NPY, expression of AgRP mRNA is also strongly induced by fasting and leptin deficiency, suggesting that AgRP and NPY gene expression are regulated in parallel within the same arcuate

nucleus neurons (63). The arcuate nucleus, therefore, appears to contain a unique neuronal subtype (NPY/AgRP neuron) that, when activated, exerts dual effects to promote hyperphagia and weight gain by activating NPY receptors on the one hand and by antagonizing melanocortin receptors on the other.

Corticotropin-releasing hormone

In addition to its well-known role as a major controller of hypothalamic-pituitary-adrenal axis activity, corticotropin-releasing hormone (CRH) is well-suited to function as a catabolic central effector molecule. Administration of this 41–amino acid peptide into the paraventricular nucleus, the primary site of CRH biosynthesis and an area with abundant CRH receptors, elicits a constellation of effects that promotes a state of negative energy balance and weight loss. These include suppression of food intake (64) coupled with stimulation of SNS outflow (64, 65), which increases lipolysis (65) and activates BAT thermogenesis (66). Moreover, chronic central CRH administration reduces food intake and body weight in normal rats (64), genetically obese rats (67), rats rendered obese by lesions to the ventromedial hypothalamic nucleus (VMN) (68), and primates (69). That endogenous CRH participates in energy homeostasis is suggested by the increase of CRH mRNA concentrations in the paraventricular nucleus documented in several conditions associated with anorexia and weight loss. These include adrenalectomy (17), involuntary overfeeding (70), and administration of leptin (34) or cytokines such as interleukin 1β (71, 72). Conversely, conditions associated with hyperphagia and activation of anabolic effector pathways, including food deprivation (73) and insulin-deficient diabetes (31), are associated with reduced CRH expression in rat hypothalamus. Changes in hypothalamic CRH signaling may therefore contribute to adaptive changes in energy balance in these conditions.

An important effect of glucocorticoids in the brain is to inhibit hypothalamic CRH expression, which may contribute to the effect of glucocorticoid excess to promote hyperphagia and weight gain (17, 74). Regulation of hypothalamic production and release of CRH may, therefore, be an important site at which glucocorticoids and leptin interact in the control of energy balance. This interaction provides a plausible explanation for the effect of adrenalectomy to increase responsiveness to leptin in a rat model (75).

Cocaine- and amphetamine-regulated transcript

Cocaine- and amphetamine-regulated transcript (CART) is widely expressed in the brain, including hypothalamic areas such as the arcuate nucleus, paraventricular nucleus, and dorsomedial hypothalamic nucleus (76, 77), and encodes a neuropeptide with potent, but short-lived anorexic effects after intracerebroventricular administration (76, 78). The finding that food intake increases after intracerebroventricular infusion of antisera raised against the CART peptide suggests that it functions as an endogenous inhibitor of feeding (78, 76). Moreover, hypothalamic expression of CART is reduced by fasting and by both genetic leptin deficiency (in ob/ob mice) and leptin resistance (in fa/fa rats) (76). Support for the hypothesis that hypothalamic CART expression is regulated by leptin was provided by a study in which leptin treatment of ob/ob mice was shown to markedly increase CART mRNA in the arcuate nucleus (76). These data suggest strongly that CART peptide is a member of the family of catabolic central effector pathways that participates in the CNS response to leptin.

ROLE OF THE AUTONOMIC NERVOUS SYSTEM IN THE CONTROL OF ENERGY BALANCE

Autonomic outflow is regulated by many of the same brain regions involved in the control of food intake. These include the lateral hypothalamic area (LHA), VMN, and paraventricular nucleus. Moreover, the effects of brain peptides and monoamines on energy expenditure and metabolism in peripheral tissues are likely to be mediated via changes in autonomic outflow (17, 18). Therefore, the autonomic nervous system seems likely to be the key efferent mechanism by which central effector pathways influence energy expenditure and metabolism. For example, activation of the SNS, which promotes energy dissipation and weight loss, can be stimulated by CRH and inhibited by NPY. Regulation of SNS outflow, therefore, may help to mediate the effect of these peptides on energy homeostasis.

Activity of the SNS increases in response to feeding (17, 79) and contributes to the thermic effect of food, ≈5–10% of daily energy expenditure (80), and involves activation of BAT in rodents. When energy intake increases, as during the consumption of a highly palatable “cafeteria” diet, thermogenesis increases proportionately via an SNS-dependent mechanism (81, 82) and thereby limits weight gain. Conversely, fasting and energy restriction reduce SNS activation of BAT and decrease energy expenditure (79). Therefore, increased SNS activity during states of positive energy balance contributes to the compensatory elevation of energy expenditure that limits excess fat storage, whereas reduced SNS tone is a component of the adaptive response to starvation. Although the mechanisms underlying regulation of SNS outflow are incompletely understood, they may involve changes in central effector pathway activity in response to changing input from adiposity-related hormones.

Although an important role for BAT thermogenesis in energy homeostasis is widely accepted, adult humans do not have discrete BAT depots. Therefore, questions exist about the role of thermogenic uncoupling in human energy homeostasis. The recent discovery that human skeletal muscle and other tissues express 2 related mitochondrial uncoupling proteins, UCP-2 and UCP-3, has generated interest in the hypothesis that control of energy expenditure in humans and other mammals involves hormonal regulation of thermogenic uncoupling at diffuse sites throughout the body (83, 84).

Many experimental models of obesity are accompanied by an impaired SNS response to food intake and other stimuli. These forms of experimental obesity are therefore proposed to result, at least in part, from an impaired SNS response to the ingestion of nutrients (17). According to this hypothesis, impairment of sympathetically mediated thermogenesis results in a diversion of ingested energy into fat stores and is therefore a major factor in the pathogenesis of obesity. This mechanism was forwarded to explain obesity in mice with transgenic ablation of BAT (85).

An alternative hypothesis, however, is that defective SNS function contributes to obesity only when it is the consequence of disordered regulation of central effector system activity. According to this proposal, a defect in thermogenesis resulting from impaired SNS activation does not, in and of itself, cause obesity. This is because the ability of increased energy efficiency to promote weight gain is limited by increased negative feedback signaling to central effector pathways that accompanies weight gain.

Thus, although reduced energy expenditure may favor a positive state of energy balance and promote weight gain, this effect should be limited by increased CNS signaling mediated by adiposity signals such as leptin and insulin. The predicted outcome of an isolated reduction of energy expenditure is the development of a new steady state of energy balance after an initial expansion of adipose mass. The degree to which weight gain occurs, according to this model, depends on the degree to which energy efficiency is increased on the one hand, and on the robustness with which the CNS responds to increased negative feedback signaling on the other hand. This hypothesis is supported by the observation that mice with impaired SNS activity due to genetic deficiency of either norepinephrine (86) or UCP-1 (87) do not develop obesity, despite unambiguous defects in thermogenesis.

How then does transgenic ablation of BAT cause obesity in mice (85)? One possibility is that obesity in these animals involves defects additional to reduced thermogenesis. Indeed, these BAT-deficient mice exhibit hyperphagia (88), suggesting that impaired negative feedback control of adiposity also exists in these mice. Consistent with this possibility, BAT-deficient mice are markedly resistant to anorexia induced by leptin (89). We therefore favor the hypothesis that reduced energy expenditure may lead to weight gain, but is unlikely to cause obesity in the absence of a defect in the CNS control of energy homeostasis.

SHORT-TERM, MEAL-RELATED FACTORS

Our model groups the many stimuli that are capable of inducing an acute change in energy balance, in a manner that is unrelated to the level of adiposity, into the category of short-term meal-related or situational factors. This grouping encompasses a wide variety of both endogenous and exogenous stimuli that range from physiologic signals generated in response to a meal to behavioral and autonomic responses to social situations or to an environmental stress (eg, the fight or flight response). It should be emphasized that although the long-term regulation of energy homeostasis serves to minimize the effect of these diverse inputs on body fat stores, the level of adiposity may be affected if a change in the input from these short-term signals is sustained over long time intervals. This is particularly true for emotional factors and for changes in diet composition, both of which may influence body weight. The extent to which such inputs influence the regulated amount of body fat may therefore depend on the degree to which compensatory changes in long-term adiposity signaling occur in response to a change in body fat. The role of short-term, meal-related signals in energy homeostasis is illustrated here by the examples of glucose utilization and gastrointestinal peptide hormones.

Glucose utilization

The concept that consumption of a meal produces changes in fuel utilization that influence single-meal food intake is supported by evidence spanning 4 decades of investigation [reviewed in (90)]. The glucostatic theory for the control of feeding, reviewed by Mayer and Thomas (91), states that the body monitors its energy needs via glucoreceptive brain neurons that are responsive to their own rate of glucose utilization. Accordingly, a fall in the level of glucose utilization by these glucose-sensitive neurons was proposed to stimulate food intake, whereas the effect of a meal to increase glucose utilization led to satiety by activating glucose-responsive neurons. These effects of glucose were proposed to take place in a "hunger center" located in the LHA, which when it has bilateral lesions causes anorexia and weight loss in rats, and in a "satiety center" located within the VMN, which, when it has bilateral lesions produces obesity. These concepts were combined into a broadly accepted proposal (92) that glucoreceptive neurons governed the activity of these dual centers in the control of feeding behavior.

This dual-center model is challenged, however, by the finding that animals with VMN lesions remain responsive to glucopenia as a stimulus for feeding (93, 94) and that after a dynamic phase of weight gain, these animals regain relatively normal patterns of food intake (95, 96). Rather than manifesting a complete failure of body weight regulation due to the absence of satiety, animals with VMN lesions simply regulate fuel stores at higher than normal rates. These observations suggest that bilateral VMN lesions interrupt one or more catabolic central effector pathways, thereby favoring a positive state of energy balance, whereas pathologic weight loss associated with bilateral LHA lesions may result from the loss of key anabolic signaling pathways. That MCH- and orexin-containing neurons are localized primarily in the dorsal aspect of the LHA raises the possibility that damage to these neuropeptide systems may contribute to the effect of LHA lesions on energy homeostasis.

Although hypoglycemia stimulates food intake, the role of glucose utilization in normal feeding is clouded by evidence that pathologic cellular glucopenia is necessary to elicit a feeding response (97, 98). Glucose-sensitive neurons, therefore, may simply be components of an emergency reflex loop that defends against acute hypoglycemia (97). However, recent studies using continuous measurements of blood glucose concentrations in rats have documented a small, transient decline in plasma glucose concentrations just before the onset of spontaneous meals. This pattern of change in circulating glucose concentrations predicts impending meals sufficiently to be potentially causal, and experimental induction of the decline in glucose is reported to initiate eating (99). The possibility that the premeal decline in glucose is a component of the anticipatory response to nutrient ingestion, rather than a signal that induces the meal, however, has yet to be excluded (100). The hypothesis that changes in blood glucose concentrations participate in normal meal initiation, therefore, requires further study.

Available data do not support the concept that the rate of CNS glucose utilization plays a major role in long-term body weight regulation. First, neither the fasting plasma glucose concentration nor the rate of whole-body glucose utilization vary with differences in body adiposity in normal humans (101, 102). These indexes are therefore unlikely to convey afferent information related to fuel stores. Moreover, whereas chronic intravenous glucose infusion suppresses food intake in normal animals, hyperglycemia occurring in insulin-deficient diabetes mellitus is associated with hyperphagia. An alternative explanation that accounts for these disparate observations is that the relation between changes in blood glucose concentrations and CNS control of energy homeostasis arise from associated changes in circulating concentrations of insulin, leptin, and glucocorticoids, rather than via altered glucose utilization per se.

Gastrointestinal peptides as satiety factors

Nutrient ingestion stimulates secretion into the bloodstream of numerous gastroenteropancreatic hormones, which helps to coordinate the digestive functions that process a meal. The cen-

tral role of gastroenteropancreatic hormones in digestion led to the hypothesis that a subset of these hormones also participates in the control of satiety. To date, many peptide hormones secreted by the gut have been shown to decrease meal size, and an important physiologic role has been suggested for the peptide cholecystokinin in the control of meal size.

In 1973, Gibbs et al (103) reported that intraperitoneal injection of cholecystokinin reduces meal size in rats. The observation that administration of cholecystokinin intraperitoneally is more effective than intravenous administration (104) suggests that targets within the abdominal cavity are important for cholecystokinin-induced satiety. Subsequently, it was found that the vagus nerve, which conveys parasympathetic activity to and fro between the brain and the gut, is a target for cholecystokinin's effects on feeding. The mechanism by which cholecystokinin promotes satiety is hypothesized to involve both inhibition of gastric emptying (105, 106), which stimulates vagal afferents sensitive to gastric distention, and direct activation of vagal afferent fibers that terminate in the brainstem. Evidence to support the latter mechanism includes the finding that cholecystokinin receptors are present on afferent vagus nerve fibers and that the satiety effect of peripherally administered cholecystokinin requires an intact abdominal vagus nerve (107, 108). Gastric vagal afferents that are responsive to cholecystokinin (109) terminate on cell bodies in the nucleus tractus solitarius (110), the primary brain area for processing afferent information from the gastrointestinal tract.

Several aspects of cholecystokinin action exemplify the distinction between short-term, meal-related factors and long-term hormonal signals that regulate adiposity. This difference is illustrated in a study in which intraperitoneal administration of cholecystokinin to free-feeding rats before each meal resulted in a consistent reduction in meal size of ≈50% (111). Rather than continuing to lose weight, however, the rats responded to this challenge by eating these smaller meals about twice as often. Despite a pronounced change in single meal size; therefore, overall food intake and body weight were essentially unaffected. The satiety effect of intraperitoneal cholecystokinin is also dependent on an intact vagus nerve (108), whereas the maintenance of normal body adiposity is not (90). Short-term signals such as cholecystokinin, therefore, do not appear to convey input to the CNS that is critical to the maintenance and defense of the level of adipose mass. Rather, their effects on energy balance can be overridden by control mechanisms that operate over long time intervals to regulate fuel stores.

Implicit in our model of energy homeostasis is a mechanism for integrating input from short-term, meal-related signals into the long-term control of energy balance. One hypothesis to explain this integration is that the response of the brain to short-term signals is influenced by the prevailing concentration of circulating adiposity signals. This hypothesis is supported by the observation that satiety induced by intraperitoneal cholecystokinin administration is potentiated by intracerebroventricular infusion of insulin (112) or systemic injection of leptin (113). Long-term controllers of energy balance, therefore, may regulate adipose stores in part by modulating the sensitivity of short-term signals such as cholecystokinin.

LONG-TERM CONTROLLERS OF ADIPOSITY

In contrast with the diverse nature of short-term signals that regulate single meal size, long-term signals involved in the control of adiposity appear to be few in number and to play a highly specialized role. These hormonal signals not only influence signaling by central effector pathways to favor a particular shift in energy balance, but they also modulate the sensitivity of the brain to afferent inputs generated in response to short-term factors. During weight loss, therefore, a reduced concentration of long-term adiposity signals is proposed to 1) diminish the efficacy of satiety-inducing inputs, 2) suppress catabolic effector pathways, and 3) activate anabolic effector pathways. This highly integrated set of responses to weight loss is proposed to stimulate feeding and to reduce energy expenditure, thereby ensuring the recovery of depleted fuel stores (114).

Leptin

The hypothesis that adipocytes secrete an adiposity-related negative feedback signal was first advanced by Kennedy (13) 46 y ago and the recent discovery of leptin has confirmed this hypothesis. Evidence supporting a major role for leptin in energy homeostasis has accumulated rapidly after an initial study (15) in which the ob gene was cloned and sequenced. The ob gene product leptin is a 164-kDa protein that is transcribed in adipocytes of a variety of species, including humans, and after cleavage of a signal peptide is secreted into the bloodstream where it circulates at concentrations proportional to body fat mass in rodents (115, 116) and humans (115, 117–121). Consistent with the hypothesis that changes in fat mass are transmitted to the CNS by changes in leptin concentrations, plasma leptin concentrations decrease after weight loss (115, 118) and are strongly correlated with leptin concentrations in cerebrospinal fluid (122).

A fundamental observation implicating leptin in body weight regulation is that leptin deficiency due to a loss-of-function mutation of the ob gene results in hyperphagia and massive obesity in ob/ob mice (Table 2). The CNS responds to the absence of leptin as it would to a poverty of fat stores: by increasing food intake, decreasing energy expenditure, and activating metabolic responses that promote the deposition of fat. Accordingly, leptin replacement in ob/ob mice should normalize body weight and composition and supranormal leptin concentrations achieved by exogenous administration should reduce fat stores. These predictions have been confirmed in studies of intravenous (123), subcutaneous (124), intraperitoneal, (125–130), and intracerebroventricular leptin administration (124, 125, 131). Complementing its anorexic effects, leptin also increases energy expenditure and normalizes the reduced metabolic rate and body temperature characteristic of ob/ob mice (127). This effect may result from SNS activation, because intravenous leptin infusion increases the firing rate of SNS nerves, which innervate muscle, BAT, kidney, and adrenal gland in anesthetized rats (132).

As occurs in mice, genetic leptin deficiency in humans is associated with profound hyperphagia and weight gain (133), and mutation of the leptin receptor is also accompanied by severe obesity in humans (134). Although impaired leptin signaling is probably a rare cause of human obesity, these data support the hypothesis that leptin plays a critical role in human body weight regulation. Abnormal neuroendocrine function accompanies mutation of the leptin receptor in humans, suggesting an important role for leptin in endocrine regulation as well as in energy homeostasis. Consistent with this hypothesis, female ob/ob and db/db mice are infertile because of hypothalamic hypogonadism. When treated with leptin, normal reproductive

function is restored to female ob/ob mice (135, 136), an effect that cannot be reproduced by weight loss alone. Similarly, leptin treatment of male ob/ob mice elevates follicle-stimulating hormone concentrations and increases testicular and seminal vesicle mass, which improves fertility (136). The finding that the effect of fasting in normal mice—suppression of the gonadotrophic, thyroid, and hypothalamic-pituitary-adrenal axes—is attenuated by leptin administration (137) suggests that leptin deficiency is a key mediator of these responses. Flier (138) has argued cogently that a falling leptin concentration is an important signal to the brain that body fuel stores are threatened and is therefore a key aspect of leptin's evolutionary function in humans.

Leptin also appears to be important for normal glucose homeostasis because leptin administration ameliorates the obesity-associated hyperinsulinemia and hyperglycemia of ob/ob mice (127). Leptin administration inhibits hepatic glycogenolysis in normal rats, an effect that is accompanied by increased fat oxidation in the liver (139). Leptin is also reported to inhibit insulin secretion via a direct effect on β cells (140). Although these studies are provocative, the importance of leptin in glucose homeostasis in normal animals remains uncertain.

Leptin targets

The finding that food intake and body weight are reduced by low doses of leptin administered into the cerebroventricular system of mice (124, 125, 141) and rats (131) suggests that its metabolic and feeding effects are mediated in the brain. Consistent with this hypothesis, leptin is present in human cerebrospinal fluid in concentrations that are strongly correlated with plasma leptin concentrations (122), and leptin receptors (also termed OB-R) are present in various brain regions including the hypothalamus (34, 142, 143). There are ≥6 splice variants of the leptin receptor (142), only 1 of which (OB-Rb) is abundantly and preferentially expressed in the hypothalamus. This long form of the leptin receptor is strongly implicated in leptin signal transduction because it contains an intracellular domain with homology to receptors of the cytokine family that appears to mediate intracellular leptin signaling via the Janus kinase—signal transducers and activators (JAK-STAT) of the transcription pathway to control gene transcription (144). The observation that OB-Rb is abnormally spliced in mice homozygous for the db mutation (db/db mice) (142), which are phenotypically identical to ob/ob mice on the same strain background (145), established an important role for the long form of the leptin receptor in body weight regulation (Table 2).

The finding that both ob/ob and db/db mice have an elevated expression of OB/Rb in the arcuate nucleus (146) suggests that leptin itself may participate in the control of hypothalamic leptin receptor gene expression. Similarly, fasting in normal rats is associated with a sharp decrease in leptin concentrations and with increased OB-Rb mRNA concentrations in the arcuate nucleus. Because ob/ob mice have increased sensitivity to the anorexic effects of leptin, changes in hypothalamic leptin receptor expression are one factor that may help to explain genetic or acquired differences in leptin responsiveness.

Both ob/ob and db/db mice overexpress the NPY gene in the arcuate nucleus (39, 40). Because prolonged administration of NPY into rodents elicits behavioral, autonomic, and metabolic responses characteristic of ob/ob and db/db mice [eg, hyperphagia, reduced energy expenditure, obesity, hyperglycemia, hyperinsulinemia, hypercortisolemia, and hypogonadism (23, 24, 147)], overproduction of hypothalamic NPY in these mice may contribute to their obesity syndrome. If leptin deficiency is the cause of overexpression of hypothalamic NPY in ob/ob mice, then leptin administration should attenuate NPY gene expression in ob/ob mice, but not in db/db mice. These predictions have been confirmed (124, 148). Evidence that NPY plays a crucial role in the pathogenesis of obesity in ob/ob mice was provided in a study in which NPY knockout mice were crossed into the ob/ob genotype (130) to create leptin-deficient mice that lack NPY; these mice have an attenuated obesity syndrome (by ≈50%). Thus, NPY is required for the complete response to leptin deficiency. This dependence of obesity in leptin-deficient mice on NPY signaling does not appear to involve the Y_5 receptor because obesity is not attenuated in ob/ob mice lacking this receptor subtype (47).

It is becoming increasingly clear, however, that NPY is but one of many hypothalamic systems that responds to leptin in the regulation of energy balance. Pathways that stimulate food intake and promote weight gain (eg, NPY, MCH, AgRP, and orexins) appear to be inhibited by leptin, activated during fasting, or both, whereas those pathways that promote anorexia and weight loss (eg, melanocortins, CART, thyrotropin-releasing hormone, and CRH) are stimulated by leptin. Thus, a highly integrated and redundant system of neuronal pathways appears to mediate the CNS response to a change in leptin signaling.

Regulation of ob gene expression and leptin secretion

In rodents, weight loss reduces both adipocyte ob gene expression and circulating leptin concentrations (115, 116, 149–152) and refeeding rapidly normalizes ob mRNA concentrations (149). Ob gene expression is elevated in most rodent models of obesity, including fa/fa obese Zucker rats (153), rats and mice with VMN lesions (116, 154), yellow obese (A^y) mice (150), mice with transgenic BAT deficiency (116), mice with knockout of the MC4 receptor (55), and mice with diet-induced obesity (125, 150, 155). Thus, excessive deposition of body fat elicits the expected increase in circulating leptin, an observation that raises the possibility that resistance to leptin may accompany most forms of rodent obesity.

Concentrations of plasma leptin and adipocyte ob mRNA in humans also decrease with weight loss (115, 118) and increase with weight gain (115). Interestingly, one study (118) found that a diet-induced reduction of 10% of body weight was associated with a 53% reduction in serum leptin concentrations when measured during the end of the weight-loss period, but that leptin concentrations tended to increase during the weight-maintenance period, despite no change in weight. This observation suggests that, in addition to the level of fat stores, leptin secretion is sensitive to changes in energy balance (156).

In humans, leptin concentrations do not change acutely with meal consumption and do not fluctuate with acute changes in endogenous insulin or glucose concentrations (117). Leptin, therefore, is not a satiety signal. Rather, circulating leptin concentrations exhibit a circadian rhythm in human subjects, being highest around midnight and lowest around noon (117). In contrast, mRNA concentrations in ob rats increase sharply during the dark phase when rats are actively eating and are lowest during the light phase (149); a similar pattern was reported for plasma leptin concentrations in mice (137). The mechanisms underlying the circadian leptin rhythm and the differences in this rhythm between rodents and humans remain unknown.

Insulin may participate in the control of leptin secretion. In rodents, ob gene expression increases after insulin administration, both without (149, 150) and with (150, 152) concomitant infusions of glucose. Insulin also exerts direct effects on adipocyte leptin synthesis and secretion (157, 158). In humans, however, short-term (up to 5 h) hyperinsulinemic, euglycemic, and hyperglycemic clamps do not stimulate increases in circulating leptin (120, 121), although leptin concentrations do increase during more prolonged insulin infusion (120). Glucocorticoids may also increase ob gene expression and leptin secretion from adipocytes (158, 159). However, a physiologic role for glucocorticoids in the control of leptin production has yet to be shown. Indeed, fasting (149, 150) and uncontrolled diabetes (160) reliably lower ob gene expression and leptin secretion despite increased circulating glucocorticoid concentrations (35). If glucocorticoids do stimulate leptin secretion, therefore, this effect can be overridden by other factors during conditions such as fasting.

Role of insulin signaling in the CNS

Like leptin concentrations, plasma insulin concentrations vary in proportion to body adiposity (10, 101, 102, 161). The hypothesis that insulin secreted from the pancreas enters the CNS, where it acts as a humoral feedback regulator of food intake and energy balance (14), was first supported by the observation that chronic intracerebroventricular insulin administration in baboons caused a dose-dependent reduction in food intake and body weight (162). This finding was subsequently confirmed in rats (31, 163, 164), sheep (165), and marmots (166). Insulin receptors (52) and related intracellular signaling molecules such as insulin receptor substrate 1, which are concentrated in hypothalamic areas such as the arcuate nucleus (167), may mediate insulin's effects on food intake. Circulating insulin enters the CNS after intravenous infusion (162, 168–172) via a saturable transport mechanism (173). The kinetics of this process are consistent with transport mediated via insulin receptors (173) expressed on the luminal surface of brain microvessels (174). The efficiency of transport via the BBB insulin receptor is sufficiently high that it has been used as a mechanism for delivery of protein pharmaceuticals that do not otherwise enter the brain. According to this strategy, the protein of interest is conjugated to an insulin receptor antibody, which greatly increases its transport across the BBB receptor in a primate model (175).

During systemic infusion, insulin's effects in the CNS to promote a state of negative energy balance are opposed by potent anabolic effects exerted in peripheral tissues. This is particularly evident in the treatment of uncontrolled insulin-dependent diabetes, whereby the normalization of blood glucose concentrations with insulin treatment causes weight gain despite reduced food intake (176). The potential for systemic insulin administration to cause weight gain contrasts sharply with the weight loss associated with central insulin infusion, even in rats with uncontrolled diabetes (31).

One mechanism by which insulin may participate in energy homeostasis is via its effect to inhibit hypothalamic expression of NPY (26, 31). Central insulin infusion also potentiates the satiety effect of peripherally administered cholecystokinin (112, 177). Elevated brain insulin concentrations may therefore promote a state of negative energy balance both by inhibiting anabolic effector pathways (eg, NPY) and by increasing sensitivity to peripheral satiety signals such as cholecystokinin.

GLUCOCORTICOID SIGNALING IN THE CNS

In peripheral tissues, glucocorticoids exert catabolic actions that promote the loss of lean body mass. In contrast, the effects of glucocorticoids on the CNS tend to be anabolic in the sense that they increase food intake and promote a state of positive energy balance. Consistent with this view, glucocorticoid deficiency induced by adrenalectomy causes anorexia and weight loss (an effect that is pronounced in most rodent forms of obesity) and these effects are reversed by glucocorticoid replacement. However, glucocorticoid excess per se does not cause a dose-dependent increase in food intake or body weight in normal animals. One potential explanation for this observation is that glucocorticoids have actions in the CNS that oppose those of insulin and leptin. Because glucocorticoid administration increases circulating insulin and leptin concentrations, any CNS action of systemically administered glucocorticoids to increase energy balance may be opposed by increased negative feedback signaling to the brain (35, 36, 178).

Because circulating glucocorticoid concentrations are sensitive to factors other than adiposity and energy balance (eg, stress), we do not view glucocorticoids as adiposity-related negative feedback signals. Rather, glucocorticoids appear to antagonize the CNS response to insulin and leptin and thereby promote a state of positive energy balance. Thus, the anorexic response to intracerebroventricular leptin (75) or insulin (179) is potentiated by adrenalectomy in rats, and this effect is reversed by glucocorticoid replacement. Furthermore, leptin and insulin inhibit hypothalamic NPY and leptin stimulates hypothalamic CRH gene expression (34), whereas glucocorticoids exert the opposite effects (17, 35, 180). These observations suggest that interactions of leptin, insulin, and glucocorticoids at the level of central effector pathways may play an important role in energy homeostasis.

CONCLUSIONS

In summary, our model of energy homeostasis proposes that long-term adiposity-related signals such as insulin and leptin influence the neuronal activity of central effector pathways that serve as controllers of energy balance. Because these hormones circulate at concentrations that are proportionate to fat mass and energy balance, a change in body fat stores sufficient to alter the delivery of these hormones to the brain induces central effector pathway responses that promote the return of adiposity to its original value. Superimposed on this long-acting control system are short-term situational and meal-related signals that arise from many sources, including the gastrointestinal tract, the environment, and higher centers in the brain. Although these inputs can exert potent effects on meal initiation, meal size, and meal frequency, their effect on body fat content is limited by compensatory changes in the level of adiposity signals. Through this mechanism, body fuel stored in the form of adipose tissue tends to remain constant despite short-term mismatches in energy balance.

REFERENCES

1. Kaiyala KJ, Woods SC, Schwartz MW. New model for the regulation of energy balance and adiposity by the central nervous system. Am J Clin Nutr 1995;62(suppl):1123S–34S.
2. Keesey RE, Powley TL. The regulation of body weight. Annu Rev Psychol 1986;37:109–33.
3. Keesey RE. A set-point theory of obesity. In: Brownell KD, Foreyt JP, eds. Handbook of eating disorders: physiology, psychology, and treatment of obesity, anorexia, and bulimia. New York: Basic

Books, 1986:63–87.
4. Stallone DD, Stunkard AJ. The regulation of body weight: evidence and clinical implications. Ann Behav Med 1991;13:220–30.
5. Drenick EJ, Johnson D. Weight reduction by fasting and semistarvation in morbid obesity: long-term follow-up. Int J Obes 1978;2:123–32.
6. Garner DM, Wooley SC. Confronting the failure of behavorial and dietary treatments for obesity. Clin Psychol Rev 1991;11:729–80.
7. Faust IM, Johnson PR, Hirsch J. Adipose tissue regeneration following lipectomy. Science 1977;197:391–3.
8. Larson KA, Anderson DB. The effects of lipectomy on remaining adipose tissue depots in the Sprague Dawley rat. Growth 1978;42:469–77.
9. Chlouverakis C, Hojnicki D. Lipectomy in obese hyperglycemic mice (ob/ob). Metabolism 1974;23:133–7.
10. Bernstein IL, Lotter EC, Kulkosky PJ. Effect of force-feeding upon basal insulin levels in rats. Proc Soc Exp Biol Med 1975;150:546–8.
11. Sims EAH. Experimental obesity, diet-induced thermogenesis and their clinical implications. Clin Endocrinol Metab 1976;5:377–95.
12. Edholm OG. Energy balance in man. J Hum Nutr 1977;31:413–31.
13. Kennedy GC. The role of depot fat in the hypothalamic control of food intake in the rat. Proc R Soc Lond B Biol Sci 1953;140:579–92.
14. Woods SC, Porte D Jr. Insulin and the set-point regulation of body weight. In: Novin D, Bray GA, Wyrwichka W, eds. Hunger: basic mechanisms and clinical implications. New York: Raven Press, 1976:273–80.
15. Zhang Y, Proenca R, Maffie M, Barone M, Leopold L, Friedman J. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425–32.
16. Woods S, Seeley R, Porte DJ, Schwartz M. Signals that regulate food intake and energy homeostasis. Science 1998;280:1378–3.
17. Bray GA, Fisler J, York DA. Neuroendocrine control of the development of obesity: understanding gained from studies of experimental animal models. Front Neuroendocrinol 1990;11:128–81.
18. Bray G. Peptides affect the intake of specific nutrients and the sympathetic nervous system. Am J Clin Nutr 1992;55(suppl):265S–71S.
19. Scheurink AJ, Steffens AB. Central and peripheral control of sympathoadrenal activity and energy metabolism in rats. Physiol Behav 1990;48:909–20.
20. Leibowitz SF. Hypothalamic neuropeptide Y, galanin, and amines: concepts of coexistence in relation to feeding behavior. In: Proceedings of the New York Academy of Sciences. New York: Academy of Sciences, 1990:221–35.
21. Stanley BG, Kyrkouli SE, Lampert S, Leibowitz SF. Neuropeptide Y chronically injected into the hypothalamus: a powerful neurochemical inducer of hyperphagia and obesity. Peptides 1986;7:1189–92.
22. Morley JE. Neuropeptide regulation of appetite and weight. Endocr Rev 1987;8:256–87.
23. Billington CJ, Briggs JE, Grace M, Levine AS. Effects of intracerebroventricular injection of neuropeptide Y on energy metabolism. Am J Physiol 1991;260:R321–7.
24. Zarjevski N, Cusin I, Vetter R, Rohner-Jeanrenaud F, Jeanrenaud B. Chronic intracerebroventricular neuropeptide-Y administration to normal rats mimics hormonal and metabolic changes of obesity. Endocrinology 1993;133:1753–8.
25. White JD, Kershaw M. Increased hypothalamic neuropeptide Y expression following food deprivation. Mol Cell Neurosci 1989;1:41–8.
26. Schwartz MW, Sipols AJ, Marks JL, et al. Inhibition of hypothalamic neuropeptide Y gene expression by insulin. Endocrinology 1992;130:3608–16.
27. Schwartz MW, Sipols AJ, Grubin CE, Baskin DG. Differential effect of fasting on hypothalamic expression of genes encoding neuropeptide Y, galanin and glutamic acid decarboxylase. Brain Res Bull 1993;31:361–7.
28. Sahu A, Kalra PS, Kalra SP. Food deprivation and ingestion induce reciprocal changes in neuropeptide Y concentrations in the paraventricular nucleus. Peptides 1988;9:83–6.
29. Leedom LJ, Meehan WP. The psychoneuroendocrinology of diabetes mellitus in rodents. Psychoneuroendocrinology 1989;14:275–94.
30. White JD, Olchovsky D, Kershaw M, Berelowitz M. Increased hypothalamic content of preproneuropeptide-Y messenger ribonucleic acid in streptozotocin-diabetic rats. Endocrinology 1990;126:765–72.
31. Sipols AJ, Baskin DG, Schwartz MW. Effect of intracerebroventricular insulin infusion on diabetic hyperphagia and hypothalamic neuropeptide gene expression. Diabetes 1995;44:147–51.
32. Kalra SP, Dube MG, Sahu A, Phelps CP, Kalra P. Neuropeptide Y secretion increases in the paraventricular nucleus in association with increased appetite for food. Proc Natl Acad Sci U S A 1991;88:10931–5.
33. Williams G, Gill JS, Lee YC, Cardoso HM, Okpere BE, Bloom SR. Increased neuropeptide Y concentrations in specific hypothalamic regions of streptozocin-induced diabetic rats. Diabetes 1989;38:321–7.
34. Schwartz MW, Seeley RJ, Campfield LA, Burn P, Baskin DG. Identification of targets of leptin action in rat hypothalamus. J Clin Invest 1996;98:1101–6.
35. Dallman MF, Strack AM, Akana SF, et al. Feast and famine: critical role of glucocorticoids with insulin in daily energy flow. Front Neuroendocrinol 1993;14:303–47.
36. Strack AM, Sebastian RJ, Schwartz MW, Dallman MF. Glucocorticoids and insulin: reciprocal signals for energy balance. Am J Physiol 1995;268:142–9.
37. Beck B, Burlet A, Nicolas JP, Burlet C. Hypothalamic neuropeptide Y (NPY) in obese Zucker rats: implications in feeding and sexual behaviors. Physiol Behav 1990;47:449–53.
38. Sanacora G, Kershaw M, Finkelstein JA, White JD. Increased hypothalamic content of preproneuropeptide Y mRNA in genetically obese Zucker rats and its regulation by food deprivation. Endocrinology 1990;127:730–7.
39. Wilding JPH, Gilbey SG, Bailey CJ, et al. Increased neuropeptide-Y messenger ribonucleic acid (mRNA) and decreased neurotensin mRNA in the hypothalamus of the obese (ob/ob) mouse. Endocrinology 1993;132:1939–44.
40. Chua SC, Brown AW, Kim J, Hennessey KL, Leibel RL, Hirsch J. Food deprivation and hypothalamic neuropeptide gene expression: effects of strain background and the diabetes mutation. Mol Brain Res 1991;11:291–9.
41. Akabayashi A, Wahlestedt C, Alexander JT, Leibowitz SF. Specific inhibition of endogenous neuropeptide Y synthesis in arcuate nucleus by antisense oligonucleotides suppresses feeding behavior and insulin secretion. Brain Res 1994;21:55–61.
42. Schaffhauser A, Stricker-Kongrad A, Brunner L, et al. Inhibition of food intake by neuropeptide Y Y5 receptor antisense oligodeoxynucleotides. Diabetes 1997;46:1792–8.
43. Stanley BG, Magdalin W, Seirafi A, Nguyen MM, Leibowitz SF. Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y_1 receptor mediating this peptide's effect. Peptides 1992;13:581–7.
44. Shibasaki T, Oda T, Imaki T, Ling N, Demura H. Injection of anti-neuropeptide Y γ-globulin into the hypothalamic paraventricular nucleus decreases food intake in rats. Brain Res 1993;601:313–6.
45. Gerald C, Walker MW, Criscione L, et al. A receptor subtype involved in neuropeptide-Y-induced food intake. Nature 1996;382:168–71.
46. Erickson JC, Clegg KE, Palmiter RD. Sensitivity to leptin and susceptibility to seizures of mice lacking neuropeptide Y. Nature 1996;381:415–8.
47. Marsh D, Hollopeter G, Kafer K, Palmiter R. Role of the Y5 neuropeptide Y receptor in feeding and obesity. Nat Med 1998;4:718–21.

48. Pedrazzini T, Seydoux J, Kunstner P, et al. Cardiovascular response, feeding behavior and locomotor activity in mice lacking the NPY Y1 receptor. Nat Med 1998;4:722–6.
49. Qu D, Ludwig DS, Gammeltoft S, et al. A role for melanin-concentrating hormone in the central regulation of feeding behaviour. Nature 1996;380:243–7.
50. Sakurai T, Amemiya A, Ishii M, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G-protein-coupled receptors that regulate feeding behavior. Cell 1998;92:573–85.
51. de Lecea L, Kilduff TS, Peyron C, et al. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci U S A 1998;95:322–7.
52. Baskin DG, Wilcox BJ, Figlewicz DP, Dorsa DM. Insulin and insulin-like growth factors in the CNS. Trends Neurosci 1988;11:107–11.
53. Jegou S, Balsquez C, Delbende C, Bunel DT, Vaudry H. Regulation of alpha-melanocyte stimulating hormone release from hypothalamic neurons. Ann N Y Acad Sci 1993;680:260–78.
54. Mountjoy K, Mortrud M, Low M, Simerly R, Cone R. Localization of the melanocortin-4 receptor (MC4-R) in neuroendocrine and autonomic control circuits in the brain. Mol Endocrinol 1994;8:1298–308.
55. Huszar D, Lynch C, Fairchild-Huntress V, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. Cell 1997;88:131–41.
56. Fan W, Boston B, Kesterson R, Hruby V, Cone R. Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. Nature 1997;385:165–8.
57. Schwartz M, Seeley R, Woods S, et al. Leptin increases hypothalamic proopiomelanocortin (POMC) mRNA expression in the rostral arcuate nucleus. Diabetes 1997;46:2119–23.
58. Cheung CC, Clifton DK, Steiner RA. Proopiomelanocortin neurons are direct targets for leptin in the hypothalamus. Endocrinology 1997;138:4489–92.
59. Seeley R, Thiele T, van Dijk G, et al. Melanocortin receptors in leptin effects. Nature 1997;390:349.
60. Cone R, Lu D, Koppula S, et al. The melanocortin receptors: agonists, antagonists, and the hormonal control of pigmentation. Recent Prog Horm Res 1996;51:287–318.
61. Shutter J, Graham M, Kinsey A, Scully S, Luthy R, Stark K. Hypothalamic expression of ART, a novel gene related to agouti, is upregulated in obese and diabetic mutant mice. Genes Dev 1997;11:593–602.
62. Ollmann M, Wilson B, Yang Y, et al. Antagonism of central melanocortin receptors in vitro and in vivo by agouti-related protein. Science 1997;278:135–8.
63. Hahn T, Breininger JF, Baskin DG, Schwartz MW. Coexpression of AgRP and NPY in fasting-activated hypothalamic neurons. Nat Neurosci 1998;1:271–2.
64. Arase K, York DA, Shimizu H, Shargil NS, Bray GA. Effects of corticotropin releasing factor on food intake and brown adipose tissue thermogenesis in rats. Am J Physiol 1988;255:E255–9.
65. Egawa H, Yoshimatsu H, Bray GA. Effect of corticotropin releasing hormone and neuropeptide Y on electrophysiological activity of sympathetic nerves to interscapular brown adipose tissue. Neuroscience 1990;34:771–5.
66. Rothwell N. Central effects of CRF on metabolism and energy balance. Neurosci Biobehav Rev 1989;14:263–71.
67. Arase K, Shargill NS, Bray GA. Effects of intraventricular infusion of corticotropin-releasing factor on VMH-lesioned obese rats. Am J Physiol 1989;256:R751–6.
68. Arase K, Shargill NS, Bray GA. Effect of corticotropin releasing factor on genetically obese (fatty) rats. Physiol Behav 1989;45:565–70.
69. Glowa J, Gold P. Corticotropin releasing hormone produces profound anorexigenic effects in the rhesus monkey. Neuropeptides 1991;18:55–61.
70. Seeley RJ, Matson CA, Chavez M, Woods SC, Dallman MF, Schwartz MW. Behavioral, endocrine, and hypothalamic responses to involuntary overfeeding. Am J Physiol 1996;271:R819–23.
71. Uehara A, Sekiya C, Takasugi Y, Namiki M, Arimura A. Anorexia induced by interleukin 1: involvement of corticotropin-releasing factor. Am J Physiol 1989;257:613–7.
72. Sapolsky R, Rivier C, Yamamoto G, Plotsky P, Vale W. Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. Science 1987;238:522–6.
73. Brady LS, Smith MA, Gold PW, Herkenham M. Altered expression of hypothalamic neuropeptide mRNAs in food restricted and food-deprived rats. Neuroendocrinology 1990;52:441–7.
74. Bray GA. Autonomic and endocrine factors in the regulation of food intake. Int J Obes 1989;13:327–35.
75. Zakrzewska KE, Cusin I, Sainsbury A, Rohner-Jeanrenaud F, Jeanrenaud B. Glucocorticoids as counterregulatory hormones of leptin. Diabetes 1997;46:717–9.
76. Kristensen P, Judge M, Thim L, et al. Hypothalamic CART is a new anorectic peptide regulated by leptin. Nature 1998;393:72–6.
77. Couceyro P, Koylu E, Kuhar M. Further studies on the anatomical distribution of CART by in situ hybridization. J Chem Neuroanat 1997;12:229–41.
78. Lambert P, Couceyro P, McGirr K, Vechia S, Smith Y, Kuhar M. CART peptides in the central control of feeding and interactions with neuropeptide Y. Synapse 1998;29:1–6.
79. Young JB, Landsberg L. Stimulation of the sympathetic nervous system during sucrose feeding. Nature 1977;269:615–7.
80. Ravussin E, Swinburn BA. Pathophysiology of obesity. Lancet 1992;340:404–8.
81. Rothwell NJ, Stock MJ. Effects of feeding a palatable 'cafeteria' diet on energy balance in young and adult lean (+/−) Zucker rats. Br J Nutr 1982;47:461–71.
82. Rothwell NJ, Stock MJ. Brown adipose tissue and diet-induced thermogenesis. In: Trayhurn P, Nicholls DG, eds. Brown adipose tissue. New York: Edward Arnold Publishers, 1986:269–98.
83. Gong DW, He Y, Karas M, Reitman M. Uncoupling protein-3 is a mediator of thermogenesis regulated by thyroid hormone, beta3-adrenergic agonists, and leptin. J Biol Chem 1997;272:24129–32.
84. Fleury C, Neverova M, Collins S, et al. Uncoupling protein-2: a novel gene linked to obesity and hyperinsulinemia. Nat Genet 1997;15:269–72.
85. Lowell BB, Susulic VS, Hamann A, et al. Development of obesity in transgenic mice after genetic ablation of brown adipose tissue. Nature 1993;366:740–2.
86. Thomas SA, Palmiter RD. Thermoregulatory and metabolic phenotypes of mice lacking noradrenaline and adrenaline. Nature 1997;387:94–7.
87. Enerback S, Jacobsson A, Simpson E, et al. Mice lacking mitochondrial uncoupling protein are cold-sensitive but not obese. Nature 1997;387:27–8.
88. Hamann A, Flier J, Lowell B. Decreased brown fat markedly enhances susceptibility to diet-induced obesity, diabetes and hyperlipidemia. Endocrinology 1996;137:21–9.
89. Hamann A, Büsing B, Kausch C, et al. Chronic leptin treatment does not prevent the development of obesity in transgenic mice with brown fat deficiency. Diabetologia 1997;40:810–5.
90. Langhans W, Scharrer E. Metabolic control of eating, energy expenditure and bioenergetics of obesity. In: Simopoulos AP, ed. World review of nutrition and dietetics. Basel, Switzerland: Karger, 1992:1–67.
91. Mayer J, Thomas DW. Regulation of food intake and obesity. Science 1967;156:328–37.
92. Stellar E. The physiology of motivation. Psychol Rev 1954;61:5–22.
93. King BM, Grossman SP. Response to glucoprivic and hydrational challenges by normal and hypothalamic hyperphagic rats. Physiol Behav 1977;18:463–73.
94. King BM, Stamoutsos BA, Grossman SP. Delayed response to 2-

deoxy-D-glucose in hypothalamic obese rats. Pharm Biochem Behav 1978;8:259–62.
95. Teitelbaum P. Disturbances in feeding and drinking behavior after hypothalamic lesions. In: Jones MR, ed. Nebraska Symposium on Motivation. Lincoln, NB: University of Nebraska Press, 1961:39–69.
96. Hoebel BG, Teitelbaum P. Weight regulation in normal and hypothalamic hyperphagic rats. J Comp Physiol Psychol 1966;61:189–93.
97. Lotter EC, Woods SC. Injections of insulin and changes of body weight. Physiol Behav 1977;18:293–7.
98. Grossman SP. The role of glucose, insulin and glucagon in the regulation of food intake and body weight. Neurosci Biobehav Rev 1986;10:295–315.
99. Campfield LA, Smith FJ. Transient declines in blood glucose signal meal initiation. Int J Obes 1990;14:15–33.
100. Woods SC, Strubbe JH. The psychobiology of meals. Psychonomic Bull Rev 1994;1:141–55.
101. Polonsky KS, Given BD, VanCauter E. Twenty-four hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. J Clin Invest 1988;81:442–8.
102. Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and B-cell function in human subjects: evidence for a hyperbolic function. Diabetes 1993;42:1663–72.
103. Gibbs J, Young RC, Smith GP. Cholecystokinin decreases food intake in rats. J Comp Physiol Psychol 1973;84:488–95.
104. Greenberg D, Smith GP. Hepatic-portal infusion reduces the satiating potency of CCK-8. Physiol Behav 1988;44:535–8.
105. Gibbs J, Smith GP. The neuroendocrinology of postprandial satiety. Front Neuroendocrinol 1984;8:223–45.
106. Moran TH, McHugh PR. Gastric and non-gastric mechanisms for satiety action of cholecystokinin. Am J Physiol 1988;4:R628–32.
107. Sankaran H, Deveney CW, Goldfine ID, Williams JA. Preparation of biologically active radioiodinated cholecystokinin for radioreceptor assay and radioimmunoassay. J Biol Chem 1979;254:9349–51.
108. Smith GP, Jerome C, Cushin BJ, Eterno R, Simansky KJ. Abdominal vagotomy blocks the satiety effect of cholecystokinin in the rat. Science 1981;213:1036–7.
109. Smith GP, Jerome E, Norgren R. Afferent axons in abdominal vagus mediate the satiety effect of cholycystokinin in rats. Am J Physiol 1985;249:R638–41.
110. Crawley JN, Kiss JZ, Mezey E. Bilateral midbrain transections block the behavioral effects of cholecystokinin on feeding and exploration in rats. Brain Res 1984;322:316–21.
111. West DB, Fey D, Woods SC. Cholecystokinin persistently suppresses meal size but not food intake in free-feeding rats. Am J Physiol 1984;246:R776–87.
112. Figlewicz DP, Stein LJ, West D, Porte D Jr, Woods SC. Intracisternal insulin alters sensitivity to CCK-induced meal suppression in baboons. Am J Physiol 1986;250:R856–60.
113. Matson CA, Wiater M, Kuiper JL, Weigle DS. Synergy between leptin and cholecystokinin (CCK) to control daily caloric intake. Peptides 1997;18:1275–8.
114. Schwartz M, Seeley R. Neuroendocrine responses to starvation and weight loss. N Engl J Med 1997;336:1802–11.
115. Maffei M, Halaas J, Ravussin E, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1995;1:1155–66.
116. Frederich RC, Hamann A, Anderson S, Lollmann B, Lowell BB, Flier JS. Leptin levels reflect body lipid content in mice: evidence for diet-induced resistance to leptin action. Nat Med 1995;1:1311–4.
117. Sinha MK, Ohannesian JP, Heiman ML, et al. Nocturnal rise of leptin in lean, obese, and non-insulin-dependent diabetes mellitus subjects. J Clin Invest 1996;97:1344–7.
118. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996;334:292–5.
119. McGregor GP, Desaga JF, Ehlenz K, et al. Radioimmunological measurement of leptin in plasma of obese and diabetic human subjects. Endocrinology 1996;137:1501–4.
120. Kolaczynski JW, Nyce MR, Considine RV, et al. Acute and chronic effect of insulin on leptin production in humans. Diabetes 1996;45:699–701.
121. Dagogo-Jack S, Fanelli C, Paramore D, Brothers J, Landt M. Plasma leptin and insulin relationships in obese and nonobese humans. Diabetes 1996;45:695–8.
122. Schwartz MW, Peskind E, Raskind M, et al. Cerebrospinal fluid leptin levels: relationship to plasma levels and to adiposity in humans. Nat Med 1996;2:589–93.
123. Rentsch JR, Levens N, Chiesi M. Recombinant ob-gene product reduces food intake in fasted mice. Biochem Biophys Res Commun 1995;214:131–6.
124. Stephens TW, Bashinski M, Bristow PK, et al. The role of neuropeptide Y in the antiobesity action of the obese gene product. Nature 1995;377:530–4.
125. Campfield L, Smith F, Gulsez Y, Devos R, Burn P. Mouse ob protein: evidence for a peripheral signal linking adiposity and central neural networks. Science 1995;269:546–9.
126. Halaas JL, Gajiwala KS, Maffel M, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. Science 1995;269:543–6.
127. Pelleymounter MA, Cullen MJ, Baker MB, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. Science 1995;269:540–3.
128. Levin N, Nelson C, Gurney A, Vandlen R, DeSauvage F. Decreased food intake does not completely account for adiposity reduction after ob protein infusion. Proc Natl Acad Sci U S A 1996;93:1726–30.
129. Weigle DS, Bukowski TR, Foster DC, et al. Recombinant ob protein reduces feeding and body weight in the ob/ob mouse. J Clin Invest 1995;96:2065–70.
130. Erickson JC, Hollopeter G, Palmiter RD. Attenuation of the obesity syndrome of ob/ob mice by the loss of neuropeptide Y. Science 1996;274:1704–7.
131. Seeley R, van Dijk G, Campfield L, et al. Intraventricular leptin reduces food intake and body weight of lean rats but not Zucker obese rats. Horm Metab Res 1997;28:664–8.
132. Haynes WG, Morgan DA, Walsh SA, Mark AL, Sivitz WI. Receptor-mediated regional sympathetic nerve activation by leptin. J Clin Invest 1997;100:270–8.
133. Montague C, Farooql I, Whitehead J, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997;387:903–8.
134. Clement K, Vaisse C, Lahlou N, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998;392:330–1.
135. Chehab FF, Lim ME, Lu R. Correction of the sterility defect in homozygous obese female mice by treatment with the human recombinant leptin. Nat Genet 1996;12:318–20.
136. Barash I, Cheung C, Weigle D, et al. Leptin is a metabolic signal to the reproduction system. Endocrinology 1996;137:3144–7.
137. Ahima R, Prabakaran D, Mantzoros C, et al. Role of leptin in the neuroendocrine response to fasting. Nature 1996;382:250–2.
138. Flier J. What's in a name? In search of leptin's physiologic role. J Clin Endocrinol Metab 1998;83:1407–13.
139. Rossetti L, Massillon D, Barzilai N, et al. Short term effects of leptin on hepatic gluconeogenesis and in vivo insulin action. J Biol Chem 1997;272:27758–63.
140. Kieffer TJ, Heller RS, Leech CA, Holz GF, Habener JF. Leptin suppression of insulin secretion by the activation of ATP-sensitive K^+ channels in pancreatic B-cells. Diabetes 1997;46:1087–93.
141. Halaas J, Boozer C, Blair-West J, Fidahusein N, Denton D, Fried-

man JM. Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. Proc Natl Acad Sci U S A 1997;94:8878–83.
142. Gwo-Hwa L, Proenca R, Montez JM, et al. Abnormal splicing of the leptin receptor in diabetic mice. Nature 1996;379:632–5.
143. Tartaglia LA, Dembski M, Weng X, et al. Identification and expression cloning of a leptin receptor, OB-R. Cell 1995;83:1263–71.
144. White D, Kuropatwinski K, Devos R, Baumann H, Tartaglia L. Leptin receptor (OB-R) signaling. J Biol Chem 1997;272:4065–71.
145. Coleman DL. Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. Diabetologia 1978;14:141–8.
146. Baskin D, Seeley R, Kuijper J, et al. Increased expression of mRNA for the long form of the leptin receptor (OB-Rb) in the hypothalamus is associated with leptin hypersensitivity and fasting. Diabetes 1998;47:535–43.
147. Stanley BG. Neuropeptide Y in multiple hypothalamic sites controls eating behavior, endocrine, and autonomic systems for energy balance. In: Colmers WF, Wahlestedt C, eds. The biology of neuropeptide Y and related peptides. Ottawa: Humana Press, 1993:457–509.
148. Schwartz MW, Baskin DG, Bukowski TR, et al. Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in ob/ob mice. Diabetes 1996;45:531–5.
149. Saladin R, De Vos P, Guerre-Millo M, et al. Transient increase in obese gene expression after food intake or insulin administration. Nature 1995;377:527–9.
150. Mizuno TM, Bergen H, Funabashi T, et al. Obese gene expression: reduction by fasting and stimulation by insulin and glucose in lean mice, and persistent elevation in acquired (diet induced) and genetic (yellow agouti) obesity. Proc Natl Acad Sci U S A 1996;93:3434–8.
151. MacDougald OA, Hwang C, Fan H, Lane MD. Regulated expression of the obese gene product (leptin) in white adipose tissue and 3T3 L1 adipocytes. Proc Natl Acad Sci U S A 1995;92:9034–7.
152. Cusin I, Sainsbury A, Doyle P, Rohner-Jeanrenaud F, Jeanrenaud B. The ob gene and insulin: a relationship leading to clues to the understanding of obesity. Diabetes 1995;44:1467–70.
153. Ogawa Y, Masuzaki H, Isse N, et als. Molecular cloning of rat obese cDNA and augmented gene expression in genetically obese Zucker fatty (fa/fa) rats. J Clin Invest 1995;96:1647–52.
154. Funahashi T, Shimomura I, Hiraoka H, et al. Enhanced expression of rat obese (ob) gene in adipose tissues of ventromedial hypothalamus (VMH)-lesioned rats. Biochem Biophys Res Commun 1995;211:469–75.
155. Frederich RC, Lollmann B, Hamann A, et al. Expression of ob mRNA and its encoded protein in rodents. J Clin Invest 1996;96:1658–63.
156. Rosenbaum M, Leibel R, Hirsch J. Regulation of energy storage, intake and expenditure. N Engl J Med 1997;337:396–407.
157. Mueller W, Gregoire F, Stanhope K, et al. Evidence that glucose metabolism regulates leptin secretion from cultured rat adipocytes. Endocrinology 1998;139:551–8.
158. Slieker LJ, Sloop KW, Surface PL, et al. Regulation of expression of ob mRNA and protein by glucocorticoids and cAMP. J Biol Chem 1996;271:5301–4.
159. De Vos P, Saladin R, Auwerx J, Staels B. Induction of ob gene expression by corticosteroids is accompanied by body weight loss and reduced food intake. J Biol Chem 1995;270:15958–61.
160. Havel P, Uriu-Hare J, Liu T, et al. Marked and rapid decreases of circulating leptin in streptozotocin diabetic rats: reversal by insulin. Am J Physiol 1998;274:R1482–91.
161. Bagdade JD, Bierman EL, Porte D Jr. The significance of basal insulin levels in the evaluation of the insulin response to glucose in diabetic and nondiabetic subjects. J Clin Invest 1967;46:1549–57.
162. Woods SC, Stein LJ, McKay LD, Porte D Jr. Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. Nature 1979;282:503–5.
163. Brief DJ, Davis JD. Reduction of food intake and body weight by chronic intraventricular insulin infusion. Brain Res Bull 1984;12:571–5.
164. Ikeda H, West DB, Pustek JJ, et al. Intraventricular insulin reduces food intake and body weight of lean but not obese Zucker rats. Appetite 1986;7:381–6.
165. Foster LA, Ames NK, Emery RS. Food intake and serum insulin responses to intraventricular infusions of insulin and IGF-I. Physiol Behav 1991;50:745–9.
166. Florant GL, Singer L, Scheurink AJ, Park CR, Richardson RD, Woods SC. Intraventricular insulin reduces food intake and body weight of marmots during the summer feeding period. Physiol Behav 1991;49:335–8.
167. Baskin DG, Sipols AJ, Schwartz MW, White MF. Immunocytochemical detection of insulin receptor substrate-1 (IRS-1) in rat brain: colocalization with phosphotyrosine. Regul Pept 1993;48:257–66.
168. Steffens AB, Scheurink AJ, Porte D Jr, Woods SC. Penetration of peripheral glucose and insulin into cerebrospinal fluid in the rat. Am J Physiol 1988;255:R200–4.
169. Schwartz MW, Bergman RN, Kahn SE, et al. Evidence for uptake of plasma insulin into cerebrospinal fluid through an intermediate compartment in dogs. J Clin Invest 1991;88:1272–81.
170. Schwartz MW, Sipols AJ, Kahn SE, et al. Kinetics and specificity of insulin uptake from plasma into cerebrospinal fluid. Am J Physiol 1990;259:E378–83.
171. Wallum BJ, Taborsky GJ Jr, Porte D Jr, et al. Cerebrospinal fluid insulin levels increase during intravenous insulin infusions in man. J Clin Endocrinol Metab 1987;64:190–4.
172. Stein LJ, Dorsa DM, Baskin DG, Figlewicz DP, Porte D Jr, Woods SC. Reduced effect of experimental peripheral hyperinsulinemia to elevate cerebrospinal fluid insulin concentrations of obese Zucker rats. Endocrinology 1987;121:1611–5.
173. Baura G, Foster D, Porte D Jr, et al. Saturable transport of insulin from plasma into the central nervous system of dogs in vivo: a mechanism for regulated insulin delivery to the brain. J Clin Invest 1993;92:1824–30.
174. Duffy KR, Pardridge WM. Blood-brain barrier transcytosis of insulin in developing rabbits. Brain Res 1987;420:32–8.
175. Wu D, Yang J, Pardridge W. Drug targeting of a peptide radiopharmaceutical through the primate blood-brain barrier in vivo with a monoclonal antibody to the human insulin receptor. J Clin Invest 1997;100:1804–12.
176. The DCCT Study Group. Weight gain associated with intensive therapy in the Diabetes Control and Complications Trial. Diabetes Care 1988;11:567–73.
177. Riedy CA, Chavez M, Figlewicz DP, Woods SC. Central insulin enhances sensitivity to cholecystokinin. Physiol Behav 1995;58:755–60.
178. Schwartz MW, Dallman MF, Woods SC. The hypothalamic response to starvation: implications for the study of wasting disorders. Am J Physiol 1995;269:R949–57.
179. Chavez M, Seeley R, Green P, Wilkinson C, Schwartz M, Woods S.