

Brain Regulation of Appetite and Satiety

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KEYWORDS

- Nervous system • Appetite • Metabolism
- Adipokine • Neuropeptide

Our survival depends on the ability to procure food for immediate metabolic needs and to store excess energy in the form of fat to meet metabolic demands during fasting. Eating behavior is stimulated by hunger, cravings, and hedonic sensations and also controlled by homeostatic processes. Knowledge of how the brain interacts with peripheral organs to control feeding and energy balance dates back to earlier descriptions of the “adiposogenital syndrome” in patients with pituitary tumors encroaching on the base of the brain.¹ Affected individuals manifested a voracious appetite, morbid obesity, and hypogonadism;¹ therefore, it was posited that the brain was critical in the negative feedback regulation of appetite and weight. The adiposogenital syndrome was subsequently recapitulated in rats by lesioning the ventromedial hypothalamus.² In contrast, lesions of the lateral hypothalamus prevented spontaneous feeding, resulting in starvation.² These seminal observations led to the concept of a “dual center model” in which the “satiety center” was located in the ventromedial hypothalamus and the “feeding center” was located in the lateral hypothalamus. It soon became apparent that the classic hypothalamic lesions were imprecise and often damaged adjacent brain regions and nerve tracts passing through.¹ Nonetheless, this concept formed the basis of later studies linking the brain and peripheral organs.

Energy balance requires an ability of the brain to detect the status of energy stores and match energy intake with expenditure. Various hypotheses have been advanced to explain the nature of metabolic signals that convey information to the brain. According to the “glucostatic hypothesis,” a fall in blood glucose in the fasted state triggers meal initiation whereas a rise in glucose terminates feeding.³ Although supported by glucoprivic studies in animals, the idea of glucose as the predominant metabolic signal was inconsistent with the tight regulation of plasma glucose concentration and the

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limited storage of glycogen in the liver and muscle. Adipose tissue, commonly called “fat,” provides the major storage of energy in mammals.

On the basis of the observation that body weight and fat are maintained at a constant level over long periods despite daily fluctuations in food intake, Kennedy⁴ proposed an “adipostatic model” in which factors released by fat target the brain to control feeding and maintain weight. This model was supported by cross-circulation (parabiosis) experiments.² In these studies, the blood vessels were joined between two rats to allow humoral factors to pass from one animal to the other. When a rat made obese through a ventromedial hypothalamic lesion was parabiosed with a normal lean rat, the latter became hypophagic and lost weight, suggesting that a signal related to obesity inhibited food intake.² This concept gained further credence following the discovery of the *obese* locus (*ob*) that encoded a circulating “satiety factor.”⁵ Deficiency of the *ob* product resulted in hyperphagia, early onset obesity, and hormonal abnormalities.⁵ Mice homozygous for the *diabetes* locus (*db*) also developed obesity.⁶ Based on parabiosis studies, *db/db* mice were shown to be insensitive to the satiety factor encoded by the *ob* locus.^{7,8} These findings were corroborated decades later by the discovery of leptin and leptin receptors.^{9,10} Leptin, insulin, and metabolic hormones related to fat stores control body weight through long-term effects on feeding and energy expenditure. On the other hand, neuronal and hormonal signals from the gastrointestinal tract control satiety and rarely impact body weight and adiposity. Food has pleasurable and rewarding qualities which drive appetite beyond metabolic needs. In the next sections, we discuss how the brain integrates metabolic signals, ensures energy homeostasis, and influences the hedonic control of feeding.

GUT-BRAIN CONNECTION

The gastrointestinal tract not only acts as a conduit for food but is also crucial for the digestion and absorption of nutrients. Visual, olfactory, and gustatory stimuli stimulate exocrine and endocrine secretions and gut motility even before food enters the mouth. Meal ingestion stimulates mechanoreceptors, resulting in a coordinated sequence of distension and propulsion to accommodate the mass of food and ensure digestion and nutrient absorption. The brain receives signals from the gastrointestinal tract through sensory nerves and the circulation.¹¹ Afferent nervous signals from mechanoreceptors (eg, for gastric stretch) and chemoreceptors (indicating changes in nutrient composition, osmolality, and pH) are transmitted via the vagus nerve to the dorsal vagal complex in the medulla, terminating in the medial and dorsomedial parts of the nucleus of the solitary tract (NTS). Other afferents end directly on distal dendrites of gastromotor vagal neurons or are relayed to the dorsal motor vagal nucleus, which innervates the entire gastrointestinal tract. Projections from the NTS and the parabrachial nucleus in the brainstem innervate the paraventricular, dorsomedial, and arcuate nuclei of the hypothalamus and the lateral hypothalamic area, central nucleus of the amygdala, and bed nucleus of the stria terminalis. NTS projection to the visceral sensory thalamus communicates with the visceral sensory cortex, which mediates the conscious perception of gastrointestinal fullness and satiety. Neurons located in the visceral sensory cortex also integrate taste sensation.

The neural connection between the gut and brain has been investigated using surgical and chemical approaches.¹¹ Gastric vagal stimulation or balloon distension induces satiety. Infusion of solutions rich in fat, carbohydrates, and proteins into the proximal small intestine reduces subsequent meal size. This effect is blocked by application of the sensory neurotoxin capsaicin to the vagus or surgical denervation.^{11–13} Surgically disrupting the sensory vagal fibers from the gut increases meal

size and duration.¹² Blockade of brainstem vagal afferent transmission using the N-methyl-d-aspartate receptor antagonist MK801 also increases meal size.¹⁴ Together, these studies demonstrate a powerful negative feedback control of vagal afferent innervation on feeding.^{11–13}

The gastrointestinal tract secretes hormones that control feeding. These peptides access the brain partly through the area postrema, a circumventricular organ located in the roof of the fourth ventricle. The area postrema is situated above the NTS, allowing neurons to respond directly to circulating gut hormones and to relay these signals to the neuronal circuits in the brainstem and forebrain.

Cholecystokinin (CCK) was the first gut-secreted peptide to be identified as a satiety factor.¹⁵ CCK decreases meal size.^{15,16} CCK1 receptor antagonists block the satiety effects of nutrient infusions into the gut and stimulate feeding in fed animals.¹⁷ Vagal nerves in the gut express CCK1 receptors and are stimulated by CCK. Chemical or surgical sensory vagotomy eliminated the satiety effects of CCK in rodents.^{12,15,16} When compared with lean Long-Evans Tokushima Otsuka (LETO) control rats, Otsuka Long-Evans Tokushima Fatty mice (OLETF) lacking functional CCK1 receptors overconsumed a high-fat diet, which resulted in obesity and diabetes.¹⁷ Hyperphagia in this animal was associated with higher expression of neuropeptide Y (NPY) in the dorsomedial nucleus of the hypothalamus.¹⁷ In contrast to these results in OLETF rats, a high-fat diet increased food intake and induced obesity to the same extent in both wild-type and CCK1 receptor knockout mice.^{17,18} Moreover, in contrast to OLETF rats, NPY gene expression did not increase in the dorsomedial nucleus in CCK1 receptor-deficient mice.¹⁷ These findings suggest that CCK1 receptors have different effects on food intake and weight in rodent species.

Glucagon-like peptide 1 (GLP-1) is cleaved from proglucagon and released from the L-cells of the intestine in response to meals.¹⁹ GLP-1 and longer-acting GLP-1 receptor agonists, such as exendin-4, decrease food intake in rodents when they are injected in the brain or peripherally.^{19,20} Presumably, these compounds target the area postrema, NTS, and paraventricular hypothalamic nucleus.^{19,20} GLP-1 has a strong incretin effect on insulin secretion; hence, the GLP-1 mimetic exenatide is used as an antidiabetic agent.^{19,20} Moreover, exenatide causes nausea in some patients. Because GLP-1 is rapidly inactivated by dipeptidyl peptidase (DPP) in the circulation, DPP-IV inhibitors have been developed to prolong the activity of GLP-1.^{19,20} Sitagliptin is currently being used for the treatment of diabetes. Unlike exenatide, DPP-IV inhibition does not substantially affect food intake or weight.

Oxyntomodulin is also derived from proglucagon and co-secreted with GLP-1 by intestinal L-cells after nutrient ingestion.^{19,20} Oxyntomodulin induces satiety, increases energy expenditure, and decreases weight.²⁰

Peptide YY (PYY)_{3–36} is the major circulating form of PYY.^{20,21} PYY_{3–36} is co-secreted with GLP-1 and oxyntomodulin. In early studies, PYY_{3–36} was reported to decrease food intake by inhibiting NPY/agouti-related peptide (AGRP) neurons in the hypothalamic arcuate nucleus via NPY-Y2 receptors;^{21,22} however, the satiety effect of PYY-36 may be minimized by stress and has not been confirmed by others.^{23,24}

Amylin is co-secreted with insulin from β -cells of the pancreas and exerts a potent antidiabetic effect.²⁰ Pramlintide, an amylin analogue, improves blood glucose and also reduces appetite and weight.²⁰

Ghrelin is a 28-amino acid peptide synthesized mainly in the stomach.^{25,26} The bioactive peptide has an O-linked octanoyl side group on the third serine residue. This modification is necessary for ghrelin's effects on feeding. Ghrelin levels increase during food deprivation in animals and before meals in humans and may serve as a critical

signal to induce hunger during fasting. Peripheral or direct administration of ghrelin into the brain stimulates feeding.²⁶ The site of action for ghrelin on feeding is thought to be the hypothalamus, where the growth hormone secretagogue receptor which mediates the cellular action of ghrelin is found in the ventromedial and arcuate nuclei, in particular neurons co-expressing NPY and AGRP.^{25,26} Ghrelin induces synaptic plasticity in the midbrain as well as the hippocampus, where ghrelin has been implicated in learning.^{27,28} Apart from stimulating food intake and promoting weight gain, ghrelin has been implicated in glucose metabolism.^{29,30} Deletion of ghrelin in mice increased basal insulin levels, enhanced glucose-stimulated insulin secretion, and improved peripheral insulin sensitivity.^{29,30} Likewise, growth hormone secretagogue receptor antagonists enhanced insulin secretion in rodents.³¹

Gut-derived peptides are attractive targets for inducing satiety and limiting meal size, but the potential for drug development is fraught with difficulty. Because gut hormones have a short half-life, stable analogues are needed, as is true for exenatide and DPP-IV inhibitors.²⁰ Gut hormones (eg, GLP-1 and CCK) may induce nausea and other gastrointestinal side effects which may limit their therapeutic use. Furthermore, because of the redundant neuronal and hormonal mechanisms in the gut, it is doubtful that targeting a limited number of peptides is a viable therapeutic approach. Indeed, genetic manipulation of anorexigenic gut hormones rarely causes overt changes in feeding, weight, and metabolism.^{29,30,32} Nevertheless, gut hormone alterations may explain the rapid effects of Roux-en-Y gastric bypass surgery to decrease weight and reverse diabetes.^{33,34} GLP-1 is increased after gastric bypass surgery and may inhibit appetite and augment insulin secretion.³⁴ Efforts are underway to target ghrelin for the treatment of anorexia and cachexia. Ghrelin antagonists have the potential for obesity and diabetes therapy.

LEPTIN-BRAIN INTERACTION

As mentioned earlier, the discovery of leptin was a major milestone in elucidation of the communication between the brain and energy stores. Leptin is expressed by adipocytes, and the concentrations of leptin in adipose tissue and plasma parallel the mass of adipose tissue and triglyceride content. Leptin is increased in obesity and falls with weight loss.^{35,36} These changes are partly mediated by insulin. Leptin is transported via a saturable process across the blood-brain barrier. Moreover, the circumventricular organs (eg, median eminence, subfornical organ, and area postrema) are permeable to leptin.³⁵ Leptin receptors, LRA to LRE, derived from alternate splicing of *lepr* mRNA have been identified.³⁶ The most abundant short leptin receptor, LRA, which lacks the cytoplasmic domain necessary for the Janus family of tyrosine kinases (JAK) signal transducer and activator of transcription (STAT) signaling, may mediate leptin transport across brain capillaries. The long leptin receptor, LRB, is highly expressed in the hypothalamus, brainstem, and several regions of the brain that control feeding, energy expenditure, and hormones.³⁵ Binding of leptin to LRB results in autophosphorylation of JAK2, phosphorylation of the tyrosine residues 985 and 1138 on LRB, activation and nuclear translocation of STAT3, and transcription of neuropeptides.³⁶ Conversely, leptin signaling is terminated when phosphorylated Tyr985 of LRB binds Src homology 2 (SH2)-containing tyrosine phosphatase-2, which activates ERK. LRB-Tyr985 also binds the suppressor of cytokine signaling (SOCS)3, which inhibits leptin signaling.³⁶ Leptin-mediated activation of STAT5 and protein-tyrosine phosphatase 1B also terminates leptin signaling.³⁶

Neuronal targets for leptin have been mapped in the brain using anatomic, pharmacologic, and molecular genetic techniques. Within the arcuate nucleus located above

the median eminence, neurons expressing NPY and AGRP are found medially, whereas neurons expressing proopiomelanocortin (POMC) (precursor of α -melanocyte stimulating hormone [MSH]) and cocaine and amphetamine-regulated transcript (CART) are located laterally. These neurons project to the paraventricular nucleus (PVN), which controls feeding and also provides preganglionic autonomic output to the brainstem. The PVN is the source of thyrotropin-releasing hormone, corticotropin-releasing hormone (CRH), and oxytocin, which regulate the pituitary gland and are also involved in energy metabolism.³⁵ NPY stimulates food intake, reduces energy expenditure, and increases weight via Y1 and Y5 receptors. Conversely, α -MSH and CART inhibit food intake and decrease weight. AGRP is an endogenous antagonist of α -MSH at the melanocortin-4 receptor; therefore, it has a net effect to increase food intake and weight. Melanin-concentrating hormone (MCH) and orexins are expressed in distinct populations of neurons in the lateral hypothalamic area. The targets of the MCH and orexin neurons include the trigeminal, facial, and hypoglossal motor nuclei that control licking, chewing, and swallowing, and the parasympathetic preganglionic nuclei in the medulla that control salivation, gut motility, and gut secretions. MCH and orexin neurons also communicate with noradrenergic neurons in the locus caeruleus, serotonergic neurons in the dorsal and median raphe nuclei, and the histaminergic tuberomammillary nucleus. These monoaminergic systems regulate arousal. In addition, the MCH and orexin neurons project diffusely to the cerebral cortex, most likely regulating complex behaviors in relation to sleep-wake cycles.

The significance of hypothalamic neuropeptides in energy homeostasis has been ascertained using gene ablation methods in mice.^{37–42} Ablation of NPY/AGRP in arcuate nucleus in adults caused rapid starvation.^{37,38} Deletion of MCH or MCH-1 receptor resulted in overactive lean mice.^{39,40} On the other hand, the lack of POMC or functional melanocortin-4 receptor caused hyperphagia and obesity.^{41,42}

Leptin regulates arcuate hypothalamic neurons directly by binding to LRB, activating JAK-STAT3 signaling, and regulating neuropeptide expression (Fig. 1). The fall in leptin during fasting induces hyperphagia and decreases energy expenditure by increasing NPY/AGRP and suppressing α -MSH and CART.^{35,36} Reduced leptin levels during fasting also stimulate MCH and orexins in the lateral hypothalamic area. Conversely, a rising level of leptin in the fed state inhibits food intake by suppressing NPY/AGRP and increasing anorexigenic peptides (eg, α -MSH and CRH).³⁵ Similar to fasting, deficiency of leptin signaling in *Lep^{ob/ob}* mice and *Lep^{db/db}* mice causes hyperphagia and impaired thermogenesis, associated with increased expression of NPY, AGRP, and MCH, and reduced expression of POMC.³⁵

As is true for other complex diseases, obesity is influenced by polygenic and environmental factors, particularly energy-dense food and a sedentary life style. Obese individuals are typically hyperleptinemic, and leptin's failure to prevent weight increase has led to the suggestion of "leptin resistance."³⁶ Diet-induced obesity in rodents is characterized by increased leptin levels, reduced leptin transport across the blood-brain barrier, and impaired leptin signaling in the hypothalamus related to induction of SOCS3.^{35,36} Deletion of SOCS3 in leptin-responsive neurons in the arcuate nucleus enhanced leptin sensitivity and protected against diet-induced obesity and diabetes.^{43,44}

Leptin exerts rapid effects on neurotransmission.⁴⁵ When it was applied to hypothalamic slices, leptin increased the frequency of action potentials in the anorexigenic POMC neurons by depolarizing a nonspecific cation channel, decreasing the inhibitory tone of γ -aminobutyric acid (GABA) released from NPY terminals in the arcuate nucleus, and hyperpolarizing NPY neurons.⁴⁵ Importantly, leptin decreased the action potential spike frequency in fasted wild-type mice and *Lep^{ob/ob}* mice, consistent with

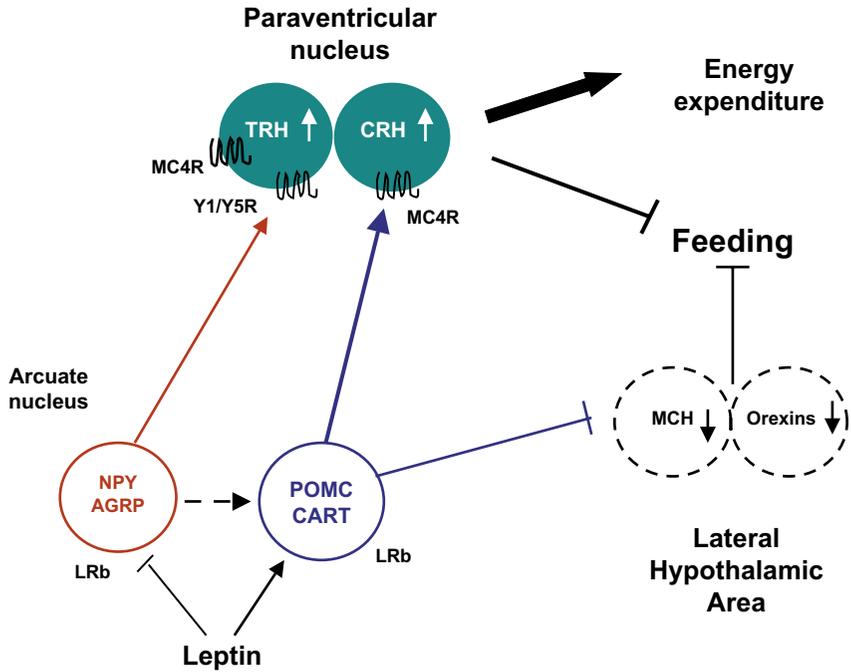


Fig. 1. Hypothalamic leptin signal transduction. Leptin inhibits NPY/AGRP and stimulates POMC/CART, resulting in an increase in anorexigenic input to the paraventricular nucleus. These changes in neuropeptide expression culminate in satiety, stimulation of energy expenditure, and weight loss.

its potent anorexigenic action.⁴⁶ The hyperphagic phenotype of *Lep^{ob/ob}* mice is characterized by an increase in the ratio of excitatory to inhibitory synapses in the hypothalamus.⁴⁷ This pattern was rapidly reversed by leptin treatment within 6 hours, suggesting that leptin-mediated synaptic plasticity preceded the appetite-suppressing effect of the hormone.⁴⁷ In contrast to leptin, the stimulatory effect of ghrelin on food intake has been associated with a net increase in synaptic activity in the hypothalamus.²⁷ These results indicate that peripheral metabolic hormones can alter brain function through modulation of synaptic function.^{27,47}

Recent studies have focused attention on the actions of leptin in the human brain.^{48–50} Rosenbaum and colleagues⁴⁸ demonstrated specific leptin-dependent changes in brain activity in response to visual food stimuli in obese patients undergoing weight reduction. Restoration of leptin levels maintained the weight reduction, as well as normalized brain activity patterns.⁴⁸ Congenital leptin deficiency is associated with reduced brain activity in regions related to hunger and increased brain activity in regions linked to satiety.^{49,50}

OTHER PERIPHERAL FACTORS CONTROLLING FEEDING AND METABOLISM

Insulin is secreted in response to meals and increases the storage of glycogen, fat, and protein. In peripheral tissues, insulin autophosphorylates the insulin receptor, leading to activation of the insulin receptor substrate (IRS) phosphatidylinositol 3-kinase (PI3K) enzyme system. Studies by Porte and colleagues,⁵¹ preceding the

discovery of leptin, revealed a blood-to-brain insulin transport and binding of insulin to several regions in the brain. Most significantly, injection of insulin into the cerebral ventricle or directly into the brain parenchyma profoundly inhibited food intake.⁵¹ We now know that insulin signaling molecules are expressed in key hypothalamic nuclei involved in energy metabolism.⁵² Insulin induces tyrosine phosphorylation of the insulin receptor and IRS-1 and -2, increases binding of activated IRS-1 and -2 to the regulatory subunit of PI3 kinase, and activates Akt (**Fig. 2**). Within the arcuate nucleus, activation of PI3 kinase by insulin occurs in neurons expressing IRS-2. Pharmacologic inhibition of PI3 kinase prevented the satiety effect of central insulin.⁵² Studies also indicate a cross-talk between leptin and insulin signaling in the hypothalamus⁵² (see **Fig. 2**). Leptin and insulin act in parallel to stimulate PI3 kinase in POMC neurons, which occurs independently of JAK-STAT3 signaling.⁵³ In addition, insulin activates PI3 kinase in AGRP neurons.⁵³ Deletion of insulin receptors in neurons resulted in a mildly obese phenotype in female mice;⁵⁴ however, it was subsequently revealed that deficiency of insulin receptors or PI3 kinase in POMC and AGRP neurons did not affect feeding or weight,^{53,55,56} suggesting that central insulin does not have a critical role in the long-term regulation of energy homeostasis.

The endocannabinoid system has significant effects on appetite and metabolism.⁵⁷ Endocannabinoids bind to cannabinoid receptors type 1 and type 2 (CB1 and CB2 receptors). The CB1 receptor, a G-protein coupled receptor, is widely expressed in the brain and peripheral tissues and is thought to mediate the metabolic actions of endocannabinoids. Overnutrition activates the endocannabinoid system, which results in hyperphagia, reduction in energy expenditure, and obesity.⁵⁷ Activation of the endocannabinoid system may contribute to development of the “metabolic syndrome,” characterized by abdominal obesity, insulin resistance, type 2 diabetes, and an increased risk of cardiovascular disease. Stimulation of CB1 receptor with anandamide increases food intake and weight in rodents. Conversely, CB1 receptor antagonists

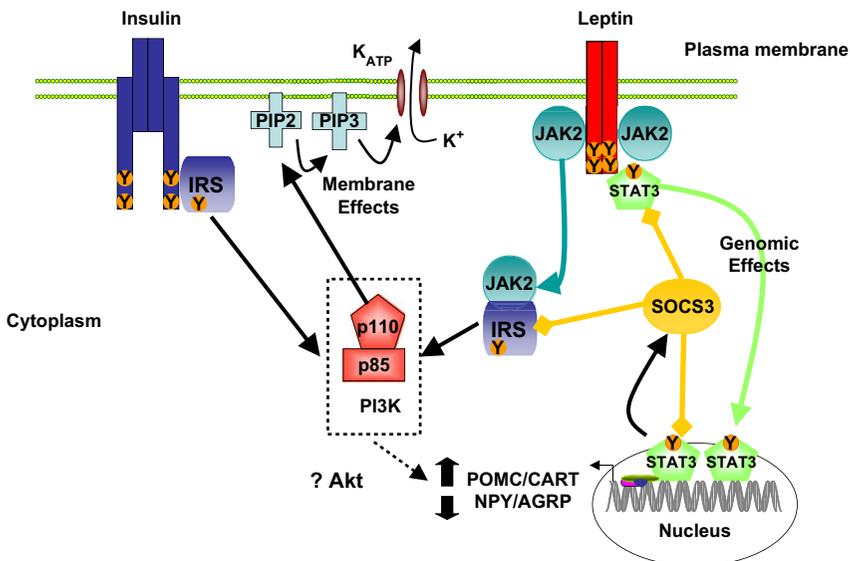


Fig. 2. Cross-talk between insulin and leptin signaling in the hypothalamus. Insulin inhibits NPY/AGRP and induces POMC/CART through activation of IRS and PI3 kinase. Leptin activates JAK2, which interacts with insulin via IRS.

suppress feeding and decrease weight.⁵⁷ Rimonabant, a CB1 receptor blocker, inhibits appetite and decreases weight in obese patients.⁵⁸ In addition, rimonabant decreases glucose and lipids.⁵⁸

Adiponectin is secreted by adipocytes and circulates in the plasma in the form of homotrimers, low-molecular weight hexamers, and high-molecular weight complexes.⁵⁹ In contrast to leptin, adiponectin is reduced in obesity and increased in response to fasting.⁵⁹ Adiponectin deficiency induces insulin resistance and hyperlipidemia and is associated with increased susceptibility toward vascular injury and atherosclerosis.⁵⁹ Insulin-sensitizing thiazolidinediones increase high-molecular weight adiponectin in humans and rodents. Adiponectin signaling is mediated via two seven-transmembrane domain-containing proteins, AdipoR1 and AdipoR2, which are widely expressed and induce AMP kinase phosphorylation and activity.⁵⁹ AdipoR1 and R2 are expressed in the brain, although adiponectin did not cross the blood-brain barrier in mice.^{59,60} Several lines of evidence support the notion that adiponectin acts centrally. Trimeric and low molecular weight adiponectin are present in cerebrospinal fluid in humans and rodents,^{61–63} and the concentration of adiponectin in cerebrospinal fluid increases following intravenous injection of adiponectin.^{62,63} Intracerebroventricular administration of adiponectin stimulated energy expenditure⁶² and reduced food intake.⁶⁴ In the latter case, adiponectin activated IRS1/2, ERK, Akt, FOXO1, JAK2, and STAT3 in the hypothalamus, indicating an overlap between the signaling of adiponectin and insulin and leptin.⁶⁴ The ability of adiponectin to decrease food intake was dependent on AdipoR1.⁶⁴ Adiponectin has been proposed as a mediator of the metabolic response to fasting.⁶³ Adiponectin when administered peripherally to mimic rising levels during fasting resulted in an increase in food intake, reduction in energy expenditure, and weight increase.⁶³ These effects were related to increases in AMP kinase activity and NPY expression in the hypothalamus.⁶³ Adiponectin also activates area postrema neurons expressing both AdipoR1 and AdipoR2 and inhibits oxytocin neurons in PVN.^{65,66} Whether these actions are involved in regulation of feeding and energy homeostasis remains to be determined.

Glucocorticoid excess increases feeding, weight, and fat.⁶⁷ When administered in the brain, glucocorticoids have a permissive action on the transcription of NPY in the hypothalamus and also modulate the levels of monoamines in the mesolimbic reward pathways to increase the consumption of palatable food.⁶⁷ In contrast, adrenalectomy decreases food intake and weight, even in the most severe form of obesity resulting from leptin deficiency.⁶⁸ Sex steroids have profound effects on appetite. Peripheral estrogen treatment enhances the anorexigenic actions of leptin and insulin in ovariectomized female rats as well as intact males.⁶⁹ Administering estradiol directly into the brain of female rats increased the sensitivity to central leptin while reducing insulin sensitivity.⁶⁹ Estradiol acted in the brain to increase subcutaneous fat.⁶⁹ The effects of estradiol on appetite and adiposity occur via estrogen receptor- α .⁷⁰

Ciliary neurotrophic factor (CNTF) induces weight loss. In rodents, CNTF inhibits food intake and increases energy expenditure, in part, through suppression of NPY;⁷¹ however, the satiety and anti-obesity affects of CNTF persist after the cessation of treatment.⁷¹ It is possible that CNTF alters the “set-point” of energy balance through long-term changes in synaptic function.⁷¹ CNTF also induces cell proliferation in mouse hypothalamus, and several of the newly formed cells are capable of responding to leptin;⁷² therefore, CNTF-induced neurogenesis may affect feeding behavior.⁷² Proinflammatory cytokines, such as tumor necrosis factor- α and interleukin-6, are involved in the pathogenesis of cachexia associated with cancer and infections. These cytokines inhibit feeding and induce thermogenesis, in part, by modulating the expression of hypothalamic neurotransmitters.^{73,74}

HEDONIC MECHANISMS REGULATING APPETITE AND SATIETY

Because eating provides energy substrates for metabolism, it is logical that eating behavior is subject to homeostatic controls described in the preceding sections; however, appetite is also driven by factors beyond physiologic needs. Food provides powerful visual, smell, and taste signals which can override satiety and stimulate feeding. We tend to overeat sweet and salty foods and consume less foods that are bitter or sour. The taste and smell of food can profoundly alter behavior; palatable food is sought after, whereas unpleasant food induces aversion. A variety of taste receptors, including the classic sweet, salty, sour, and bitter tastes, are expressed by taste cells in the tongue and oral cavity, which convey the information to the NTS and parabrachial nucleus in the brainstem. Taste sensation is then relayed to the thalamus and lateral frontal cerebral cortex, central nucleus of the amygdala, and lateral hypothalamus area. Neuropeptides implicated in the signaling of taste include substance P, CCK, and opioids. Leptin is able to modulate taste perception, as evidenced by an increased response to sweet taste in mice lacking leptin.⁷⁵ Conversely, leptin treatment decreases sweet taste signaling in *Lep^{ob/ob}* mice.⁷⁵

Psychotropic drugs affect feeding and weight.⁷⁶ Studies in animals have suggested that drug and food rewards share similar neuronal pathways. For example, the ability of AGRP to increase feeding is blocked by naloxone, an opioid antagonist.⁷⁷ Enkephalin or β -endorphin deficiency reduces the motivation for bar pressing behavior to facilitate food reward.⁷⁸ Injection of μ and κ opioid antagonist into the nucleus accumbens inhibits feeding.⁷⁶ Serotonin (5-HT_{2C} receptor) agonist inhibits food intake partly by activating melanocortin-4 receptors.⁷⁹ In mice, leptin inhibits the motivation to feed by activating dopamine and GABA-expressing neurons in the mesolimbic pathway.^{80,81} A similar action has been observed in patients with congenital leptin deficiency whereby brain activity is increased in the ventral striatum, associated with an increase in the drive to eat even when the patient has just eaten.⁵⁰ Leptin treatment reverses the “hedonic pattern” of brain activity.⁵⁰

SUMMARY

Eating behavior is critical for the acquisition of energy substrates. As discussed in this review, the gut-brain axis controls appetite and satiety via neuronal and hormonal signals. The entry of nutrients in the small intestine stimulates the release of peptides which act as negative feedback signals to reduce meal size and terminate feeding. Hormones and cytokines secreted by peripheral organs exert long-term effects on energy balance by controlling feeding and energy expenditure. Neurons involved in the homeostatic regulation of feeding are located mainly in the hypothalamus and brainstem. In addition, neuronal circuits in the limbic system mediate the motivational and reward aspects of feeding. Insights into how peripheral metabolic signals interact with the brain will be gained from brain imaging and metabolic studies in humans and preclinical experimentation in animal models using molecular, genetic, physiologic, and behavioral tools. Knowledge of the neurobiologic basis of eating will promote the understanding and rational treatment of disorders of energy homeostasis such as obesity and cachexia.

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