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# Central and Peripheral Regulation of Food Intake and Physical Activity: Pathways and Genes

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## Abstract

A changing environment and lifestyle on the background of evolutionary engraved and perinatally imprinted physiological response patterns is the foremost explanation for the current obesity epidemic. However, it is not clear what the mechanisms are by which the modern environment overrides the physiological controls of appetite and homeostatic body-weight regulation. Food intake and energy expenditure are controlled by complex, redundant, and distributed neural systems involving thousands of genes and reflecting the fundamental biological importance of adequate nutrient supply and energy balance. There has been much progress in identifying the important role of hypothalamus and caudal brainstem in the various hormonal and neural mechanisms by which the brain informs itself about availability of ingested and stored nutrients and, in turn, generates behavioral, autonomic, and endocrine output. Some of the genes involved in this "homeostatic" regulator are crucial for energy balance as manifested in the well-known monogenic obesity models. However, it can be clearly demonstrated that much larger portions of the nervous system of animals and humans, including the cortex, basal ganglia, and the limbic system, are concerned with the procurement of food as a basic and evolutionarily conserved survival mechanism to defend the lower limits of adiposity. By forming representations and reward expectancies through processes of learning and memory, these systems evolved to engage powerful emotions for guaranteed supply with, and ingestion of, beneficial foods from a sparse and often hostile environment. They are now simply overwhelmed with an abundance of food and food cues no longer contested by predators and interrupted by famines. The anatomy, chemistry, and functions of these elaborate neural systems and their interactions with the "homeostatic" regulator in the hypothalamus are poorly understood, and many of the genes involved are either unknown or not well characterized. This is regrettable because these systems are directly and primarily involved in the interactions of the modern environment and lifestyle with the human body. They are no less "physiological" than metabolic-regulatory mechanisms that have attracted most of the research during the past 15 years.

The trend to increasing rates of obesity, particularly in children, appears to be unbroken, and the most effective treatment of severe obesity currently available is obesity surgery. To solve this most alarming and untenable situation, strong action is needed very soon. Despite significant advances in understanding the regulation of energy balance and the control of food intake, no "magic bullet" pharmacological treatment is available, and no comprehensive environmental and behavioral strategies are in place to prevent this disease. Our current understanding of energy balance regulation suggests a handful of extremely important genes and their products whose malfunction leads inevitably to severe obesity in a small percentage of the population (monogenic obesity) and thousands of genes that can potentially combine to cause obesity in a much larger percentage of the population (common obesity). Clearly,

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understanding how common obesity works goes a long way in finding pharmaceutical targets and personalized dietary and behavioral strategies that could halt the epidemic.

The purpose of this review is to provide an overview of pathways and underlying genes that have already been implicated or are potentially important in energy balance regulation. After a brief overview of the multiple systems controlling energy balance, we will review structure and function of each of the key players in more detail and discuss the most attractive and promising genes as potential therapeutic targets.

## Overview of Multiple Systems Controlling Energy Intake and Expenditure

Under steady-state conditions, all fuels ingested (energy intake) are normally metabolized to maintain basic metabolic rate, thermogenesis, and muscle action (energy expenditure) (Figure 1). Excess fuels are stored as fat and used later. To maintain balance, a neural regulator senses fuel availability in the internal milieu (nutrient sensing) and generates appropriate signals to the neural circuits controlling food intake and energy expenditure, usually referred to as homeostatic regulation of adiposity and body weight.

### Major mechanisms and factors determining energy balance

Environment and lifestyle can influence both food intake and energy expenditure—in the obesogenic environment of the modern industrialized societies, there is strong pressure to increase food intake and decrease physical activity. The pressures on food intake find a fertile ground in the cognitive, hedonic/reward, and emotional neural processes that evolved in a restrictive environment where food was in shorter supply and procuring it often required considerable work. Additional pressures on energy expenditure came with the motorization, automatization, and the built environment. To maintain energy balance under these influences, the homeostatic regulator is asked to work beyond its normal range and purpose. It is an important basic dictum of this review that all of the peripheral and neural processes that make up this highly complex system are subject to individual predisposition through genes and/or changes in “wiring” through early life experience (Figure 1).

Key peripheral components are the gustatory system and the gastrointestinal tract, as well as the pancreas, liver, muscle, and adipose tissue (Figure 2). All these components are in intimate bidirectional communication with the brain through either neural connections provided by the autonomic nervous system, or hormones and metabolites. In the brain, the three major players are the caudal brainstem, the hypothalamus, and parts of the cortex and limbic system, but many other brain areas are also involved.

Highly schematic diagram showing major components and flow of information of the peripheral and central systems involved in energy balance, regulation, and control of food intake. CNS, central nervous system.

The caudal brainstem is the first relay station for nutritionally relevant information from the taste buds and the gastrointestinal tract mediated by gustatory and vagal afferents, respectively. It also contains the oromotor machinery for ingesting food and key autonomic motor neurons responsible for handling nutrients by the alimentary canal and all other abdominal organs, as well as for nonshivering thermogenesis in brown adipose tissue.

The hypothalamus, particularly the arcuate nucleus (ARC), is a major hub for integrating nutritionally relevant information originating from all peripheral organs and mediated through circulating hormones and metabolites and/or neural pathways from mainly the brainstem. Nutritional information is then further integrated with other important information from the internal and external world, such as the diurnal clock and the presence of predators. Nutritional

information also competes with other motivated behaviors such as thermoregulatory, fluid homeostatic, reproductive, and aggressive/defensive behaviors represented in the hypothalamus. Finally, the resulting optimal adaptive responses chosen are executed through behavioral, autonomic, and endocrine output pathways originating mainly in the paraventricular nucleus and lateral hypothalamus.

Cortico-limbic systems allow animals and humans to interact with the food-providing environment. Major factors operating during the foraging and procurement phase are experience, availability, and cost. Factors operating during the consummatory phase are cephalic and postingestive feed-forward mechanisms such as the sight, smell, and taste (flavor, palatability) of already familiar foods. Other factors include social context as well as ethnic and religious habits and rules. The many changes in environment and modern lifestyle that put pressure on food intake and energy balance have been discussed elsewhere (1,2,3,4,5).

The most important mechanisms and participating gene products for each of these key components are discussed in more detail in the following sections.

## Sensing of the Internal Milieu

### Taste: beyond the classic modalities

After ingestion of food, nutrient sensing starts in the oral cavity with taste receptors (Figure 3). Significant progress in taste perception came with the discovery of the gene families and signaling mechanisms responsible for detecting sweet, sour, bitter, and savory (umami) foods by taste receptor cells in the oral cavity (6,7,8,9,10,11), see ref. 12 for review. A small family of three G-protein-coupled receptors—T1R1, T1R2, and T1R3—have been validated as receptors for sweets and amino acids, indicating beneficial foods. The heterodimeric combination of T1R2+3 was validated as the sweet receptor and the T1R1+3 combination as the amino-acid (or umami) taste receptor. The bitter taste of many potentially harmful toxins is mediated by a family of ~30 G-protein-coupled receptors—the T2R family of receptors. Both of these receptor families use the heterotrimeric G-protein α-gustducin ($G\alpha_{12}$), phospholipase C-β2 (PLC-β2), and the transient receptor potential channel TRPM5 as downstream intracellular signaling cascade leading to activation of sensory nerve fibers. Salt taste is mediated through amiloride-sensitive $Na^+$ channels, and sour taste is mediated by a member of the TRP ion channels, PKD2L1, expressed in a separate population of taste receptor cells (see ref. 12 for review). Although the fatty-acid translocator CD36 and the potassium channel KV 1.5 have been identified in taste receptor cells and found to be involved in the detection of fat in rodents (10,13), a fat taste receptor has not quite yet reached the status of the other taste receptors (14,15).

Nutrient sensing in the alimentary canal and the control of food intake. Simplified schematic diagram showing the major pre- and postabsorptive transduction sites and mechanisms for the detection of ingested food and its macronutrient components. Nutrient information is sent to the brain through vagal and taste afferents (heavy dotted lines) or through the blood circulation (full lines). Specific receptors expressed by vagal afferent neurons are shown in rectangular boxes. Specific sensor mechanisms demonstrated for glucose, amino acids/proteins, and lipids/fatty acids are shown by gray, striped, and white squares, respectively. CCK, cholecystokinin; GHS-R, ghrelin receptor; GLP-1, glucagon-like peptide-1; IL-1, interleukin-1; PYY, peptide YY; TNF-α, tumor necrosis factor-α.

**Gastrointestinal tract—**Chemo- and mechanosensory mechanisms provide a good estimate of the considerable amount of nutrients that can be temporarily stored in the gastrointestinal tract. These mechanisms provide important information to the brain regarding energy that will soon be available for metabolism. Although the importance of gut—brain communication in

the short-term control of food intake has long been appreciated, its potential to also play an important role in longer-term control of appetite and energy balance has only recently emerged from animal studies and observations in patients with gastric bypass surgeries. Only the most significant mechanisms will be briefly discussed here, and the reader should consult reference (16) for a recent review.

Nutrients stored in the stomach are perceived by vagal stretch and tension sensors, with the acid-sensing ion channel ASIC3 and probably additional ion channels acting as mechanosensitive transducers (17). Neurotrophic factors such as brain-derived neurotrophic factor and neurotrophin-3, which are essential for vagal afferent innervation of the stomach wall, have also been shown to play a role in meal-taking behavior with possible longer-term effects on energy balance (18).

Ghrelin is the other important signal originating in the stomach. It is mainly secreted from oxyntic gland cells in the mucosa of the empty stomach, and secretion is rapidly suppressed upon the ingestion of food (19,20). The ghrelin receptor is expressed by a subset of stomach innervating vagal afferent neurons in the nodose ganglia (21,22), and at least in one report in vagotomized rats (21) and in patients with vagotomy (23), ghrelin's appetite-stimulating effect was abolished. However, a more careful analysis in rats with selective vagal deafferentation could not confirm these findings (24), suggesting that the major route of gastric ghrelin to the brain for the control of appetite is the bloodstream.

In the upper small intestine, cholecystokinin (CCK) appears to be the major hormonal signal with relevance to food intake control. Luminal fat and protein, but not glucose, are strong releasers of CCK from enteroendocrine cells. The food intake suppressive effect results from CCK acting in a paracrine fashion on CCKA-receptors located on vagal sensory nerve terminals in the mucosal lamina propria (25,26,27). The presence of glucose in the lumen may be signaled to the brain through the sodium—glucose cotransporter (SGLT), the release of 5-HT from another set of enteroendocrine cells, and the 5-HT3 receptor located on vagal afferent nerve terminals (28,29,30), or may alternatively use the glucose transporter 2 (GLUT2) transporter and T1R receptors also found in the intestine (31,32).

In the lower small intestine and colon, two other hormones, peptide YY (PYY) and glucagon-like peptide-1 (GLP-1), are secreted through direct luminal nutrient stimulation and neural reflexes originating in the upper small intestine. PYY is rapidly cleaved into the truncated form PYY [3–36] by dipeptidyl peptidase-IV (33). PYY [3–36] has a high affinity for the NPY2 receptor and anorexigenic potency in both rats and humans (34,35,36,37,38). Vagal afferents may be involved in the anorectic effects of PYY [3–36], as abdominal vagotomy abolished both the anorectic effect and c-fos expression in the ARC following peripherally administered PYY [3–36] (39). The NPY2 receptor is expressed in at least some vagal afferents (39,40, 41), and PYY stimulates firing of gastric vagal afferents (39).

GLP-1, also secreted from L-cells, is the site-specific splice product of the *proglucagon* gene. Not unlike PYY, GLP-1 release also appears to be stimulated by all three macronutrients by both an indirect, partly neural reflex originating in the upper small intestine and by direct mucosal contact in the lower gut (42,43,44). GLP-1 actions on pancreatic hormone secretion and gastric emptying make it a powerful regulator of glycemic homeostasis (45,46,47).

Peripheral administration of GLP-1 or its stable analog exendin-4, the naturally occurring peptide from the Gila monster lizard, enhances satiation and reduces food intake in humans and rats (48,49). Because of rapid breakdown by dipeptidyl peptidase-IV, endogenously secreted GLP-1 has a very short half-life in plasma. Thus, although endogenous GLP-1 may partly act as a true hormone through the circulation on feeding circuits in the brain, it could also act in a paracrine fashion on vagal afferent nerve fibers within the gut mucosa. This view

is supported by observations that GLP-1 receptor is expressed in the nodose ganglion, and GLP-1 increases cytosolic $Ca^{2+}$ and evokes action potentials in vagal afferent neurons (50, 51).

Discussing the gut, energy balance, and genes, one should mention the association of gut microbes with obesity. Because the obese microbiome has an increased capacity to harvest energy from the diet, it is likely to contribute to the obese state (52), and it has been speculated that the combined gene pool involved in this microbiome may exceed the gene pool of the host.

### Portal vein and liver

Except for longer chain fatty acids reaching the general circulation through lymph vessels, absorbed nutrients are collected in the hepatic portal vein and first reach the liver, the most important metabolic factory in the body. The wall of the portal vein is innervated by vagal afferent fibers (53) that act as glucosensors (54,55,56). They have been implicated in the hypoglycemia-induced sympathoadrenal (57,58) and feeding responses (59), and in the satiating properties of glucose in the presence of insulin (60,61). More recently, vagal afferent portal vein glucosensors that are also sensitive to GLP-1 have also been implicated in the food intake-suppressing effects of high protein diets mediated by intestinal gluconeogenesis (62).

The liver itself provides some information about availability of fuels that is used by the brain for the control of food intake, but the role of primary afferent nerve fibers is controversial. There are studies showing that changes in fatty-acid oxidation and adenosine triphosphate production are reflected in hepatocyte membrane potential and electrical activity of vagal afferent neurons (63,64) (for reviews, see refs. (59,65)).

### Pancreas, adipose tissue, and muscle

Pancreatic β-cells also have glucose sensing capabilities, and signaling to the brain by their secretory products insulin and amylin are thus encoding glucose availability. Insulin acts directly on the hypothalamus and other brain areas (see next section), and amylin acts to decrease food intake and gastric emptying through receptors in the area postrema and ascending pathways to the hypothalamus and limbic structures (66,67).

With the discovery of leptin, the existence and importance of direct signals from white adipose tissue, the major site of stored energy, to the brain has become clear. How leptin affects the brain is discussed in detail in the next section below. Besides leptin, adipose tissue releases additional messengers such as adiponectin, resistin, and the cytokines tumor necrosis factor-α and interleukin-1, which have all been demonstrated to signal to the brain and other peripheral organs involved in the control of energy balance (68).

In summary, a great number of mechanisms and pathways are in place to sense the availability of fuels and nutrients at all levels of assimilation. There are still many questions regarding nutrient specificity, exact location, and mode of communication to the brain for these sensors. Also note that the important role these sensors play in the metabolic and nutrient-partitioning functions of peripheral organs has not been discussed here. Let us now look at how the brain deals with this flood of information.

## Hypothalamic Integration of Nutritional and Other Relevant Information

### Neuropeptides and transmitters

Two populations of neurons, one expressing the powerfully orexigenic peptides NPY and AGRP and the other expressing the anorexigenic peptides proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), located in the ARC of the

hypothalamus are the primary integrators of various nutritional information (Figure 4). Both populations are directly and differentially sensitive not just to circulating leptin, but also to other hormones including insulin, ghrelin, and PYY [3–36], as well as to circulating metabolites including glucose, fatty acids, and amino acids. NPY/AgRP and POMC/CART neurons interact on several levels.

Hypothalamic peptidergic circuitry related to feeding and energy balance. Highly simplified diagram showing the two known neuron populations in the arcuate nucleus sensitive to signals of fuel availability and their projections to other key neuron populations orchestrating the adaptive behavioral, autonomic, and endocrine responses. CART, cocaine- and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; GABA, γ-aminobutyric acid; MCH, melanin concentrating hormone; α-MSH, α-melanocyte-stimulating hormone; PVN, paraventricular nucleus.

One is the local inhibition of POMC neurons via local axon collaterals from NPY neurons (69,70). Since NPY neurons can also produce γ-aminobutyric acid, if activated, they inhibit POMC neurons through both NPY1- and γ-aminobutyric acid-A-receptors. In the absence of reciprocal inhibition of NPY neurons by POMC neurons, this arrangement may be interpreted as a fail-safe system to protect eating as the default mode of action. A second level of interaction occurs at downstream target neurons, as NPY/AgRP and POMC projections frequently converge on common downstream sites both within and outside the hypothalamus. The melanocortin-4 and melanocortin-3 receptors are particularly significant, as melanocortin-4 receptor deficiency induces profound obesity, hyperphagia, and hyperglycemia (71), and is currently the most common monogenetic cause of human obesity (72).

The major projection sites are second-order neuron populations in the lateral/perifornical hypothalamic area (LHA) and the paraventricular nucleus of the hypothalamus (PVH). These two brain regions are classically associated with the regulation of food intake and autonomic output, and each contains a variety of neuropeptide-expressing neurons associated with energy balance control. The prevailing model suggests that input from NPY/AGRP neurons is opposed by input from POMC neurons, this “metabolic” information is integrated with input from additional brain areas, and these downstream neurons in turn project widely to third- and higher-order neurons located in many areas of the brain and spinal cord (73).

Neurons within the LHA receiving direct input from the ARC contain several food regulatory neuropeptides including orexin/hypocretin, melanin concentrating hormone, CART, neurotensin, and histamine (Figure 4). Specific populations of LHA neurons also express leptin receptors, and some are sensitive to glucose. In addition to this metabolic information, the LHA also receives information from brain areas associated with reward, motivation, learning and memory, and from brainstem areas associated with vagal and visceral sensory input, sensorimotor coordination, and arousal. In turn, these peptidergic second-order LHA neurons project widely through the entire brain (73), from the cortex to the spinal cord (Figure 4).

Second-order neurons in the PVH are classically associated with autonomic and neuroendocrine functions. Thyrotropin-releasing hormone and corticotropin-releasing hormone neurons receive direct input from both types of ARC neurons, and regulate the thyroid and HPA axis and stress response, respectively (74).

In addition to the LHA and PVH, arcuate POMC/CART neurons also project to a variety of additional areas. For example, leptin-sensitive POMC neurons project directly to brainstem areas associated with the response to satiety signals and autonomic outflow (75,76).

**Molecular integrators—**As progress has been made in defining the intracellular-signaling pathways mediating the effects of these various hormonal, transmitter, and metabolite signals, it becomes apparent that the richness of these intracellular-signaling pathways and their coupling to changes in neuronal excitability, peptide expression, and synaptic connectivity, may provide the major substrate for integrative processes (Figure 5). Leptin engages a number of intracellular pathways, including those associated with cAMP, MAPK, STAT3, and PI3K (69,77,78,79,80,81,82,83,84). STAT3 and PI3K have garnered the most attention, because obesity occurs when leptin is unable to activate STAT3, and leptin's effects on food intake and sympathetic nervous system activity are attenuated upon loss of PI3K signaling (85,86).

Molecular mechanisms of integration of various signals by hypothetical "nutrient-sensing neurons" in the mediobasal hypothalamus. AMPK, adenosine monophosphate-activated kinase; ATP, adenosine triphosphate; GABA, γ-aminobutyric acid; mTOR, mammalian target of rapamycin.

Two of the most exciting new players in intraneuronal integration are adenosine monophosphate (AMP)-activated kinase (AMPK) and the mammalian target of rapamycin (mTOR). AMPK is an evolutionarily conserved serine—threonine kinase which responds to changes in cellular energy levels (87). AMPK is sensitive to the AMP/adenosine triphosphate ratio, such that depletion of cellular energy stores activates AMPK signaling. While in peripheral tissues, AMPK activation leads to rigorous defense of cellular energy availability through increased oxidation; in the ARC, AMPK activation increases food intake and energy conservation (88). Glucose, leptin, and insulin each inhibit (88,89), and ghrelin increases, hypothalamic AMPK activity (90). However, since selectively AMPK-α2-deficient POMC and AGRP neurons exhibit normal leptin and insulin action but absent responses to changes in extracellular glucose levels, it is unlikely that AMPK acts as a general sensor of nutrient availability (91).

mTOR is another evolutionarily conserved energy sensor that has assumed a specific functional role in hypothalamic regulation of energy balance (92). In many peripheral tissues, mTOR plays a key role in coupling cellular energy status and growth factor signaling to protein synthesis, growth and div on. Recent data indicate that mTOR is expressed within key populations of mediobasal hypothalamic neurons and is sensitive to metabolic state, and that the ability of amino acids to suppress food intake and regulate neuropeptide expression may depend on mTOR (92,93). Evidence also suggests that hypothalamic mTOR contributes to leptin action, with leptin-activating hypothalamic mTOR and inhibition of mTOR blocking leptin-dependent suppression of food intake (92). Considering that insulin is also a classic regulator of mTOR signaling, likely via activation of PI3K, this activation of mTOR by leptin may reflect a downstream effect of PI3K signaling. While this work is very preliminary, it suggests that mTOR, much like AMPK, represents a potential site of convergence for both hormonal and nutrient sensing. To add to this complexity, there is also strong evidence for an interaction between AMPK and mTOR (94).

## Modulation of hypothalamic integration by circadian rhythms

The relationship between feeding, metabolism, and circadian time was strikingly highlighted when the disruption of clock genes (Clock, *Bmal*1) produced mice with obesity, hyperphagia, and abnormal glucose homeostasis (95,96). Components of the clock appear to directly regulate genes controlling behavior and metabolism, while metabolism conversely alters the expression of clock genes. This reciprocal molecular relationship is mirrored in physiology and behavior, as feeding behavior is clearly influenced by circadian time, yet nutrient ingestion is also sufficient to entrain certain circadian rhythms. These observations highlight a research area that provides a physiological and molecular framework to explain the coordinated regulation of both behavior and metabolism and also provides mechanistic support for evidence that the

disruption of circadian patterns produces alterations in ingestive behavior and metabolism (97).

### Leptin and neurotrophic factors involved in hypothalamic development, plasticity, and neurogenesis

The fact that most neurons are nonrenewable led to the assumption that the brain is essentially hardwired. However, recent findings suggest that there is a considerable degree of structural plasticity, including neural circuits involved in energy balance regulation. It was first discovered that leptin-deficient (ob/ob) mice differed from wild-type mice in the numbers of excitatory and inhibitory synapses and postsynaptic currents onto NPY/AGRP and POMC/CART neurons. Within 6 h of leptin treatment, the synaptic density normalized, and a few hours later food intake started to decrease. Similar effects of leptin could be repeated in wild-type mice after an overnight fast and refeeding, suggesting that part of leptin's effect on food intake is not mediated by acute signaling but rather by plastic structural changes (98,99).

In addition, the crucial projections of arcuate NPY and POMC neurons to second-order neurons in the PVH and other hypothalamic areas are underdeveloped in leptin-deficient mice but can be rescued by leptin treatment at an early age but not later in life (100). These findings suggest that leptin, similar to sex steroid hormones (101), plays a neurotrophic role in the development of the hypothalamus and its functions.

It is unclear what the mechanisms of these neurotrophic actions are, but the involvement of neurotrophic factors is likely. Brain-derived neurotrophic factor and its cognate tyrosine kinase receptor TrkB are increasingly implicated in energy balance regulation, as heterozygous ablation or point mutations invariably lead to an obese, hyperphagic syndrome (102,103,104, 105). It remains to be determined to what extent these changes are produced by aberrant development of the relevant neural circuits or to acute changes in signaling characteristics. Reduced food intake and increased energy expenditure following direct administration of brain-derived neurotrophic factor into the brain of adult rats suggest direct signaling effects (106,107), but changes in wiring in mutation models have not yet been examined.

## Neural Mechanisms Dealing With External Information and Conditions

### Procurement and foraging behavior: importance of learning and memory and sharpened senses

It can be clearly demonstrated that large portions of the nervous system of animals and humans are concerned with the procurement of food as a basic and evolutionarily conserved survival mechanism to defend the lower limits of adiposity. By learning about food sources and forming memorial representations including reward expectancies, these systems evolved to engage powerful emotions for guaranteed supply with, and ingestion of, beneficial foods from a sparse and often hostile environment.

One of the fundamental neurological paradigms involved is finding a good food source, remembering it, and finding it again. As simple as this sounds, it is a neurological tour de force, with just about the entire brain participating. A key structure is the hippocampal formation, known to be involved in the formation, storage, and recall of spatial and other memories (Figure 6). The gut hormone ghrelin has been shown to directly act on hippocampal neurons and induce formation of new synapses in the CA1 region, resulting in enhanced spatial learning (108). Ghrelin-deficient mice exhibited impaired spatial learning that was corrected by ghrelin administration (108). These findings are consistent with the idea that ghrelin is involved in the appetitive phase of ingestive behavior when it is important to find food in the environment. It is plausible that the ghrelin-induced changes in hippocampal function facilitate the recall of stored representations of previous experience with food. This is indicated by human subjects

reporting a vivid, plastic image of their preferred meal upon intravenous ghrelin infusion (109). These actions on hippocampal function might also be responsible for increased locomotor activity seen after ghrelin administration in rats and decreased activity in ghrelin-deficient (110) and ghrelin receptor—deficient mice (111).

Highly simplified schematic diagram showing the multiple neural systems and pathways controlling food intake, energy expenditure, and energy balance, with emphasis on interactions between “metabolic,” “cognitive,” and “rewarding” brain systems.

Ghrelin may also influence foraging behavior through activation of transcription factors. The importance of the evolutionarily conserved brain-specific homeobox transcription factor Bsx in appetitive behavior was demonstrated in a study by Sakkou *et al*. (112). Bsx is found in arcuate NPY/AgRP neurons, where it regulates expression of those peptides. In Bsx-deficient or Bsx mutant mice, NPY and AgRP expression was markedly downregulated. Bsx mutant mice exhibited greatly attenuated fasting-induced upregulation of NPY and AgRP, hyperphagia, and locomotor activity compared to that seen in wild-type mice upon fasting. These findings suggest that Bsx-mediated upregulation of NPY and AgRP is essential for foraging and appetitive behavior. The high degree of conservation of the homeobox in Bsx further highlights its evolutionary importance in the regulation of food acquisition and survival of the species (112).

Sensory perception is another function that needs to work well during foraging for food. Olfactory perception, e.g., is modulated by orexin and leptin (113,114). While leptin decreases, orexin increases the ability to smell potential food (115). Leptin (ob/ob) and leptin receptor (db/db)—deficient mice find buried food ~10 times faster than wild-type mice, and this difference disappears after injection of leptin in ob/ob mice (116). These findings suggest that low levels or absence of leptin-signaling dramatically heightens olfactory detection of food.

A role for orexin in foraging behavior is indicated by several observations. ARC NPY neurons project to orexin neurons in the LH (117,118). Orexin increases both food intake and locomotor activity (as reviewed in ref. 119), and caloric restriction enhances orexin’s effects on food intake (120). Indeed, orexin is thought to be the ideal neuropeptide to regulate foraging behavior because it enables searching for food while remaining vigilant to dangers in the environment (121).

## Hedonics and reward: liking and wanting of foods

Reward from food is processed by a complex neural system that includes the nucleus accumbens and ventral pallidum in the ventral striatum, the ventral tegmental area located in the midbrain and projecting through the mesolimbic dopamine system back to the nucleus accumbens, the prefrontal cortex, the hippocampus, and amygdala (Figure 6).

Besides neural circuits in the hindbrain, the nucleus accumbens and ventral pallidum in the limbic forebrain are key components of the distributed neural network mediating “liking” of palatable foods. The μ-opioid receptor appears to play a crucial role. Local injection of the selective μ-opioid receptor agonist DAMGO into the nucleus accumbens elicits voracious food intake, particularly of palatable sweet or high-fat foods (122,123,124), while microinjection of a selective μ-opioid receptor antagonist reduced sucrose drinking (125). To consciously experience and give subjective ratings of pleasure from palatable foods (liking), humans appear to also use areas in the prefrontal and cingulate cortex (126).

Although “liking” a food is typically followed by “wanting” and eating it, “wanting” is a dissociable process that has a distinct underlying neural substrate. This distinction grew mainly out of research on drug addiction, where stimuli that are often no longer “liked” are still

intensely “wanted” (127,128). Dopaminergic projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex, the mesolimbic dopamine system, are the most crucial components of the implicit or unconscious “wanting” system (129,130,131). Manipulation of this dopamine system powerfully influences “wanting” (instrumental performance for and consumption of) drugs or food, but not “liking” (127,132,133,134). The lateral hypothalamus is also involved in “wanting,” as electrical stimulation of this area induces rats to vigorously self-stimulate and eat (“want”) food, even though it does not make them “like” the food more (135).

Nutritionally relevant hormones can modulate activity of the mesolimbic dopamine system thought to be responsible for the wanting of food. Leptin can directly inhibit mesolimbic dopamine neurons and suppress food intake, and local inhibition of leptin signaling does the reverse (136,137,138). Neural activity in the nucleus accumbens elicited by visual food stimuli is very high in genetically leptin-deficient adolescents and promptly returns to normal levels upon leptin administration. While in the leptin-deficient state, nucleus accumbens activation was positively correlated with ratings of liking in both the fasted and fed state, it was correlated only in the fasted state after leptin treatment and in normal individuals (139).

On the other hand, ghrelin activates dopamine neurons in the ventral tegmental area, increases dopamine turnover in the nucleus accumbens, and directly stimulates food intake when locally administered (140,141). Since local ghrelin receptor blockade in the ventral tegmental area blunted rebound feeding following fasting (140), these observations suggest that enhancement of reward processing in the mesolimbic dopamine system is an integral part of endogenous ghrelin’s orexigenic action.

## Executive control of food intake and physical activity

Cortico-limbic mechanisms of reward appear to be under executive control of the prefrontal cortex. The prefrontal cortex receives sensory information from inside and outside the body as well as emotional and cognitive information from the limbic system, and it is intimately connected to cortical areas involved in motor planning and execution (Figure 6). It is thus in an ideal position to translate all available homeostatic and environmental information into adaptive behavioral responses—in brief, to make choices and dec ons (142,143).

The right prefrontal cortex appears to play a critical role in behavioral restraint and moral self-control by keeping reward-generating mechanisms in check. Damage to the right frontal cortex can lead to a general disregard for the long-term adverse consequences of behavioral choices, such as increased risk taking and excessive food intake (144). A “Gourmand syndrome,” with passion for eating highly palatable foods, was reported in two case studies of humans with damage to the right frontal hemisphere (145,146). It is interesting to speculate that part of this asymmetry is based on the asymmetries in the peripheral autonomic nervous system re-representing homeostatic activity in the dorsal posterior insula, known to be densely connected with the prefrontal cortex (147,148).

Modern neuroimaging studies also support the importance of a balanced control by distinct areas of the prefrontal cortex in the control of food intake. Successful dieters who have significantly higher levels of dietary restraint than nondieters show increased neural activity in the right dorsolateral prefrontal cortex in response to food consumption (149). In contrast, obese subjects show less activation of the left dorsolateral prefrontal cortex in response to food (150), and patients suffering from the Prader—Willi syndrome, who show severe disturbances in appetite control resulting in hyperphagia and obesity, show increased activity in the ventromedial prefrontal cortex when viewing pictures of food after glucose consumption (151). This latter finding is consistent with a role of the ventromedial prefrontal cortex in the

mediation of food intake driven by conditioned (learned) motivational cues in sated rats (152).

## How is Energy Intake and Expenditure Coordinated Under Different Conditions?

An important feature of homeostatic energy balance regulation is that both arms of the effector (intake and expenditure) can be used to achieve the desired corrective response. To efficiently correct an energy deficit, intake should be stimulated and expenditure suppressed (anabolic mode), and the reverse should happen (catabolic mode) to correct an energy surplus. While this balanced response pattern appears straightforward, its neurological organization is somewhat complicated by at least two factors. First, energy expenditure can be achieved through several mechanisms, each with its own neural controls. Basal metabolism, thermogenesis, and physical activity are each controlled by vastly different pathways and effector organs. Furthermore, thermogenesis itself is a multifaceted process with several effector organs and control circuits, and physical activity has a spontaneous and a voluntary component with fundamentally different neural pathways. Second, certain environmental and metabolic conditions may require exceptions to the basic response pattern. In the following, we will discuss homeostatic response patterns and their potential underlying mechanisms for the two most different conditions: coping with an energy deficit in the "natural" habitat, and coping with an energy surplus in today's obesogenic environment.

### Coping with an energy deficit in the "natural," restricted environment

A routine decrease in fuel availability (such as after a day in the burrow or a night at sleep) will be signaled to the brain by elevated ghrelin levels and low levels of all other gut hormones and a dip in leptin levels. With depleted glycogen stores, the major energy source will be from fatty-acid oxidation, except for the brain, which continues to oxidize glucose and lactate. Thus, arcuate NPY/AGRP neurons are active, and POMC neurons are suppressed. When the environment is considered safe, foraging begins with ghrelin facilitating the retrieval of stored memorial representations of former experience with food and loading of appropriate spatial maps into the hippocampus. Orexin neurons and other arousal systems will be activated, thereby augmenting sympathetic tone to muscle and heart and sharpening external senses. The combination of high ghrelin and low leptin will sensitize the mesolimbic dopamine system to "go for" the food represented in the retrieved memory. This activity may require considerable muscle work with the necessary energy derived from fat oxidation, but because muscle work produces heat, no energy is needed to maintain body temperature. The parasympathetic nervous system is gradually turned on to prepare the gut for the incoming nutrients. After the food is encountered and eaten, ghrelin levels drop and leptin levels rise rapidly, together with a number of additional gastrointestinal satiation signals such as distension, CCK, PYY [3–36], GLP-1, and amylin. After finding safety, the sympathetic nervous system and orexin arousal system are turned off rapidly, and metabolism switches back to fat storage and glucose oxidation. Satiety may be maintained for a certain time beyond the end of nutrient absorption from the gut by the lower gut hormones PYY [3–36] and GLP-1 and by continued high glucose availability. Eventually, fat oxidation returns and the cycle starts anew.

### Coping with an energy surplus in the modern environment of plenty

Metabolic signals relating to an energy surplus (such as normal leptin levels) will trigger several compensatory changes to maintain energy balance. The obvious behavioral changes necessary to adequately respond to an excess of energy include decreased food intake and increased physical activity, either in the form of spontaneous physical activity (SPA) or voluntary physical activity, or what is commonly thought of as "exercise." SPA and subsequent nonexercise associated thermogenesis in humans have been linked to resistance to weight gain

following forced caloric intake (153). Because SPA demonstrates the largest degree of variability of all the determinants of energy expenditure, it has been suggested that pharmaceutical interventions to enhance SPA may in the future be used to treat overweight and obesity (154). Conversely, voluntary physical activity has been found to be essential for the maintenance of lowered body weight following weight loss, according to surveys of those who have successfully maintained their weight loss for at least 5 years (155).

The importance of voluntary physical activity in the regulation of body weight can be seen in studies using *Nhlh2*- deficient mice. The Nhlh2 basic helix—loop—helix transcription factor colocalizes with thyrotropin-releasing hormone in the paraventricular nucleus and with POMC in the ARC. Its expression is regulated by energy balance, being downregulated by food deprivation and stimulated by both food intake and leptin administration (156). A study examining the pattern of weight gain in Nhlh2-deficient mice demonstrated that the mice exhibited reduced voluntary physical activity before becoming obese, and subsequent increased food intake to maintain a higher body weight (157). Clearly, identifying genes such as *Nhlh2*, or its downstream effectors, that promote voluntary physical activity will afford us a greater understanding of how to more effectively harness voluntary physical activity as a weight-loss tool.

Leptin, in addition to its inhibitory effects on food intake and stimulation of metabolic rate, can stimulate physical activity to maintain energy balance. Leptin-mediated increases in α-melanocyte-stimulating hormone and CART both increase physical activity, as suggested by pharmacological administration of CART and MCR agonists and antagonists (158,159,160, 161) and transgenic mouse models (162,163). Elevated physical activity may in turn reinforce the suppression of food intake. Access to a running wheel both reduced food intake and prevented obesity in OLETF rats, effects that were associated with increased corticotropin-releasing factor mRNA expression in the dorsomedial hypothalamus (164).

In addition to its role in foraging behavior, orexin is poised to regulate physical activity in response to an energy surplus. Orexin administered into several sites (i.e., PVH, LH, and nucleus accumbens) promotes SPA (165,166,167). It has been hypothesized that sensitivity to orexin-induced SPA is responsible for the resistance to diet-induced obesity seen in some rats (165,166). However, orexin may also be involved in foraging or appetitive behavior (see above) because it has been shown that caloric restriction enhanced orexin's effects on food intake (120).

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## REFERENCES

1. Hill JO, Peters JC. Environmental contributions to the obesity epidemic. Science 1998;280:1371–1374. [PubMed: 9603719]
2. Hill JO, Wyatt HR, Reed GW, Peters JC. Obesity and the environment: where do we go from here? Science 2003;299:853–855. [PubMed: 12574618]
3. Levitsky DA. The non-regulation of food intake in humans: hope for reversing the epidemic of obesity. Physiol Behav 2005;86:623–632. [PubMed: 16263145]
4. Rolls BJ. The supersizing of America: portion size and the obesity epidemic. Nutr Toda 2003;38:42–53.

5. Ulijaszek SJ. Human eating behaviour in an evolutionary ecological context. Proc Nutr Soc 2002;61:517–526. [PubMed: 12691181]
6. Zhang Y, Hoon MA, Chandrashekar J, et al. Coding of sweet, bitter, and umami tastes: different receptor cells sharing similar signaling pathways. Cell 2003;112:293–301. [PubMed: 12581520]
7. Adler E, Hoon MA, Mueller KL, et al. A novel family of mammalian taste receptors. Cell 2000;100:693–702. [PubMed: 10761934]
8. Nelson G, Hoon MA, Chandrashekar J, et al. Mammalian sweet taste receptors. Cell 2001;106:381–390. [PubMed: 11509186]
9. Zhao GQ, Zhang Y, Hoon MA, et al. The receptors for mammalian sweet and umami taste. Cell 2003;115:255–266. [PubMed: 14636554]
10. Laugerette F, Passilly-Degrace P, Patris B, et al. CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions. J Clin Invest 2005;115:3177–3184. [PubMed: 16276419]
11. Huang AL, Chen X, Hoon MA, et al. The cells and logic for mammalian sour taste detection. Nature 2006;442:934–938. [PubMed: 16929298]
12. Chandrashekar J, Hoon MA, Ryba NJ, Zuker CS. The receptors and cells for mammalian taste. Nature 2006;444:288–294. [PubMed: 17108952]
13. Gilbertson TA. Gustatory mechanisms for the detection of fat. Curr Opin Neurobiol 1998;8:447–452. [PubMed: 9751657]
14. Bachmanov AA, Beauchamp GK. Taste receptor genes. Annu Rev Nutr 2007;27:389–414. [PubMed: 17444812]
15. Mattes RD. Effects of linoleic acid on sweet, sour, salty, and bitter taste thresholds and intensity ratings of adults. Am J Physiol Gastrointest Liver Physiol 2007;292:G1243–G1248. [PubMed: 17290007]
16. Berthoud HR, Morrison C. The brain, appetite, and obesity. Annu Rev Psychol 2008;59:55–92. [PubMed: 18154499]
17. Page AJ, Brierley SM, Martin CM, et al. Different contributions of ASIC channels 1a, 2, and 3 in gastrointestinal mechanosensory function. Gut 2005;54:1408–1415. [PubMed: 15987792]
18. Fox EA. A genetic approach for investigating vagal sensory roles in regulation of gastrointestinal function and food intake. Auton Neurosci 2006;126-127:9–29. [PubMed: 16677865]
19. Cummings DE, Purnell JQ, Frayo RS, et al. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 2001;50:1714–1719. [PubMed: 11473029]
20. Cummings DE. Ghrelin and the short- and long-term regulation of appetite and body weight. Physiol Behav 2006;89:71–84. [PubMed: 16859720]
21. Date Y, Murakami N, Toshinai K, et al. The role of the gastric afferent vagal nerve in ghrelin-induced feeding and growth hormone secretion in rats. Gastroenterology 2002;123:1120–1128. [PubMed: 12360474]
22. Burdyga G, Varro A, Dimaline R, Thompson DG, Dockray GJ. Ghrelin receptors in rat and human nodose ganglia: putative role in regulating CB-1 and MCH receptor abundance. Am J Physiol Gastrointest Liver Physiol 2006;290:G1289–G1297. [PubMed: 16423919]
23. le Roux CW, Neary NM, Halsey TJ, et al. Ghrelin does not stimulate food intake in patients with surgical procedures involving vagotomy. J Clin Endocrinol Metab 2005;90:4521–4524. [PubMed: 15914532]
24. Arnold M, Mura A, Langhans W, Geary N. Gut vagal afferents are not necessary for the eating-stimulatory effect of intraperitoneally injected ghrelin in the rat. J Neurosci 2006;26:11052–11060. [PubMed: 17065447]
25. Raybould HE, Glatzle J, Freeman SL, et al. Detection of macronutrients in the intestinal wall. Auton Neurosci 2006;125:28–33. [PubMed: 16504594]
26. Geary N. Endocrine controls of eating: CCK, leptin, and ghrelin. Physiol Behav 2004;81:719–733. [PubMed: 15234177]
27. Smith GP, Jerome C, Norgren R. Afferent axons in abdominal vagus mediate satiety effect of cholecystokinin in rats. Am J Physiol 1985;249:R638–R641. [PubMed: 4061684]

28. Freeman SL, Bohan D, Darcel N, Raybould HE. Luminal glucose sensing in the rat intestine has characteristics of a sodium-glucose cotransporter. Am J Physiol Gastrointest Liver Physiol 2006;291:G439–G45. [PubMed: 16675747]
29. Morales M, Wang SD. Differential composition of 5-hydroxytryptamine3 receptors synthesized in the rat CNS and peripheral nervous system. J Neurosci 2002;22:6732–6741. [PubMed: 12151552]
30. Wu XY, Zhu JX, Gao J, Owyang C, Li Y. Neurochemical phenotype of vagal afferent neurons activated to express C-FOS in response to luminal stimulation in the rat. Neuroscience 2005;130:757–767. [PubMed: 15590158]
31. Dyer J, Salmon KS, Zibrik L, Shirazi-Beechey SP. Expression of sweet taste receptors of the T1R family in the intestinal tract and enteroendocrine cells. Biochem Soc Trans 2005;33:302–305. [PubMed: 15667333]
32. Mace OJ, Affleck J, Patel N, Kellett GL. Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2. J Physiol 2007;582:379–392. [PubMed: 17495045]
33. Eberlein GA, Eysselein VE, Schaeffer M, et al. A new molecular form of PYY: structural characterization of human PYY (3-36) and PYY (1-36). Peptides 1989;10:797–803. [PubMed: 2587421]
34. Larhammar D. Structural diversity of receptors for neuropeptide Y, peptide YY and pancreatic polypeptide. Regul Pept 1996;65:165–174. [PubMed: 8897639]
35. Batterham RL, Cowley MA, Small CJ, et al. Gut hormone PYY (3-36) physiologically inhibits food intake. Nature 2002;418:650–654. [PubMed: 12167864]
36. Chelikani PK, Haver AC, Reidelberger RD. Intravenous infusion of peptide YY (3-36) potently inhibits food intake in rats. Endocrinology 2005;146:879–888. [PubMed: 15539554]
37. Chelikani PK, Haver AC, Reeve JR Jr, Keire DA, Reidelberger RD. Daily, intermittent intravenous infusion of peptide YY (3-36) reduces daily food intake and adiposity in rats. Am J Physiol Regul Integr Comp Physiol 2006;290:R298–R305. [PubMed: 16210414]
38. Batterham RL, Heffron H, Kapoor S, et al. Critical role for peptide YY in protein-mediated satiation and body-weight regulation. Cell Metab 2006;4:223–233. [PubMed: 16950139]
39. Koda S, Date Y, Murakami N, et al. The role of the vagal nerve in peripheral PYY3-36-induced feeding reduction in rats. Endocrinology 2005;146:2369–2375. [PubMed: 15718279]
40. Zhang X, Shi T, Holmberg K, et al. Expression and regulation of the neuropeptide Y Y2 receptor in sensory and autonomic ganglia. Proc Natl Acad Sci USA 1997;94:729–734. [PubMed: 9012853]
41. Ghilardi JR, Allen CJ, Vigna SR, McVey DC, Mantyh PW. Cholecystokinin and neuropeptide Y receptors on single rabbit vagal afferent ganglion neurons: site of prejunctional modulation of visceral sensory neurons. Brain Res 1994;633:33–40. [PubMed: 8137166]
42. Anini Y, Hansotia T, Brubaker PL. Muscarinic receptors control postprandial release of glucagon-like peptide-1: *in vivo* and *in vitro* studies in rats. Endocrinology 2002;143:2420–2426. [PubMed: 12021207]
43. Herrmann C, Goke R, Richter G, et al. Glucagon-like peptide-1 and glucose-dependent insulin-releasing polypeptide plasma levels in response to nutrients. Digestion 1995;56:117–126. [PubMed: 7750665]
44. Herrmann-Rinke C, Voge A, Hess M, Goke B. Regulation of glucagon-like peptide-1 secretion from rat ileum by neurotransmitters and peptides. J Endocrinol 1995;147:25–31. [PubMed: 7490533]
45. Schirra J, Goke B. The physiological role of GLP-1 in human: incretin, ileal brake or more? Regul Pept 2005;128:109–115. [PubMed: 15780430]
46. Ritzel R, Orskov C, Holst JJ, Nauck MA. Pharmacokinetic, insulinotropic, and glucagonostatic properties of GLP-1 [7-36 amide] after subcutaneous injection in healthy volunteers. Dose-response-relationships. Diabetologia 1995;38:720–725. [PubMed: 7672496]
47. D'Alessio DA, Prigeon RL, Ensinck JW. Enteral enhancement of glucose disposition by both insulin-dependent and insulin-independent processes. A physiological role of glucagon-like peptide I. Diabetes 1995;44:1433–1437. [PubMed: 7589851]
48. Gutzwiller JP, Goke B, Drewe J, et al. Glucagon-like peptide-1: a potent regulator of food intake in humans. Gut 1999;44:818–816.

49. Chelikani PK, Haver AC, Reidelberger RD. Intravenous infusion of glucagon-like peptide-1 potently inhibits food intake, sham feeding, and gastric emptying in rats. Am J Physiol Regul Integr Comp Physiol 2005;288:R1695–R1706. [PubMed: 15718384]
50. Nakagawa A, Satake H, Nakabayashi H, et al. Receptor gene expression of glucagon-like peptide-1, but not glucose-dependent insulinotropic polypeptide, in rat nodose ganglion cells. Auton Neurosci 2004;110:36–43. [PubMed: 14766323]
51. Kakei M, Yada T, Nakagawa A, Nakabayashi H. Glucagon-like peptide-1 evokes action potentials and increases cytosolic Ca2+ in rat nodose ganglion neurons. Auton Neurosci 2002;102:39–44. [PubMed: 12492134]
52. Turnbaugh PJ, Ley RE, Mahowald MA, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006;444:1027–1031. [PubMed: 17183312]
53. Berthoud HR, Kressel M, Neuhuber WL. An anterograde tracing study of the vagal innervation of rat liver, portal vein and biliary system. Anat Embryol (Berl) 1992;186:431–442. [PubMed: 1280009]
54. Niijima A. Glucose-sensitive afferent nerve fibres in the hepatic branch of the vagus nerve in the guinea-pig. J Physiol 1982;332:315–323. [PubMed: 7153929]
55. Burcelin R, Da Costa A, Drucker D, Thorens B. Glucose competence of the hepatoportal vein sensor requires the presence of an activated glucagon-like peptide-1 receptor. Diabetes 2001;50:1720–1728. [PubMed: 11473030]
56. Burcelin R, Dolci W, Thorens B. Glucose sensing by the hepatoportal sensor is GLUT2-dependent: *in vivo* analysis in GLUT2-null mice. Diabetes 2000;49:1643–1648. [PubMed: 11016447]
57. Hevener AL, Bergman RN, Donovan CM. Novel glucosensor for hypoglycemic detection localized to the portal vein. Diabetes 1997;46:1521–1525. [PubMed: 9287058]
58. Hevener AL, Bergman RN, Donovan CM. Portal vein afferents are critical for the sympathoadrenal response to hypoglycemia. Diabetes 2000;49:8–12. [PubMed: 10615943]
59. Friedman MI. An energy sensor for control of energy intake. Proc Nutr Soc 1997;56:41–50. [PubMed: 9168519]
60. Friedman MI, Tordoff MG, Ramirez I. Integrated metabolic control of food intake. Brain Res Bull 1986;17:855–859. [PubMed: 3801940]
61. Stricker EM, Rowland N, Saller CF, Friedman MI. Homeostasis during hypoglycemia: central control of adrenal secretion and peripheral control of feeding. Science 1977;196:79–81. [PubMed: 841345]
62. Mithieux G, Misery P, Magnan C, et al. Portal sensing of intestinal gluconeogenesis is a mechanistic link in the diminution of food intake induced by diet protein. Cell Metab 2005;2:321–239. [PubMed: 16271532]
63. Horn CC, Tordoff MG, Friedman MI. Role of vagal afferent innervation in feeding and brain Fos expression produced by metabolic inhibitors. Brain Res 2001;919:198–206. [PubMed: 11701132]
64. Lutz TA, Niijima A, Scharrer E. Intraportal infusion of 2,5—anhydro-D-mannitol increases afferent activity in the common hepatic vagus branch. J Auton Nerv Syst 1996;61:204–208. [PubMed: 8946344]
65. Langhans W. Role of the liver in the control of glucose-lipid utilization and body weight. Curr Opin Clin Nutr Metab Care 2003;6:449–455. [PubMed: 12806220]
66. Young A. Inhibition of gastric emptying. Adv Pharmacol 2005;52:99–121. [PubMed: 16492543]
67. Lutz TA, Mollet A, Rushing PA, Riediger T, Scharrer E. The anorectic effect of a chronic peripheral infusion of amylin is abolished in area postrema/nucleus of the solitary tract (AP/NTS) lesioned rats. Int J Obes Relat Metab Disord 2001;25:1005–1011. [PubMed: 11443499]
68. Trayhurn P, Wood IS. Signalling role of adipose tissue: adipokines and inflammation in obesity. Biochem Soc Trans 2005;33:1078–1081. [PubMed: 16246049]
69. Cowley MA, Smart JL, Rubinstein M, et al. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. Nature 2001;411:480–484. [PubMed: 11373681]
70. Roseberry AG, Liu H, Jackson AC, Cai X, Friedman JM. Neuropeptide Y-mediated inhibition of proopiomelanocortin neurons in the arcuate nucleus shows enhanced desensitization in ob/ob mice. Neuron 2004;41:711–722. [PubMed: 15003171]
71. Butler AA. The melanocortin system and energy balance. Peptides 2006;27:281–290. [PubMed: 16434123]

72. Farooqi S, O'Rahilly S. Genetics of obesity in humans. Endocr Rev 2006;27:710–718. [PubMed: 17122358]

73. Berthoud H-R. Multiple neural systems controlling food intake and body weight. Neurosci Biobehav Rev 2002;26:393–428. [PubMed: 12204189]

74. Lechan RM, Fekete C. The TRH neuron: a hypothalamic integrator of energy metabolism. Prog Brain Res 2006;153:209–235. [PubMed: 16876577]

75. Zheng H, Patterson LM, Phifer CB, Berthoud HR. Brainstem melanocortinergic modulation of meal size and identification of hypothalamic POMC projections. Am J Physiol Regul Integr Comp Physiol 2005;289:R247–R258. [PubMed: 15746303]

76. Berthoud HR, Sutton GM, Townsend RL, Patterson LM, Zheng H. Brainstem mechanisms integrating gut-derived satiety signals and descending forebrain information in the control of meal size. Physiol Behav 2006;89:517–524. [PubMed: 16996546]

77. Munzberg H, Myers MG Jr. Molecular and anatomical determinants of central leptin resistance. Nat Neurosci 2005;8:566–570. [PubMed: 15856064]

78. Schwartz MW, Seeley RJ, Campfield LA, Burn P, Baskin DG. Identification of targets of leptin action in rat hypothalamus. J Clin Invest 1996;98:1101–1106. [PubMed: 8787671]

79. Schwartz MW, Seeley RJ, Woods SC, et al. Leptin increases hypothalamic pro-opiomelanocortin mRNA expression in the rostral arcuate nucleus. Diabetes 1997;46:2119–2123. [PubMed: 9392508]

80. Spanswick D, Smith MA, Groppi VE, Logan SD, Ashford ML. Leptin inhibits hypothalamic neurons by activation of ATP-sensitive potassium channels. Nature 1997;390:521–525. [PubMed: 9394003]

81. Niswender KD, Morton GJ, Stearns WH, et al. Intracellular signalling. Key enzyme in leptin-induced anorexia. Nature 2001;413:794–795. [PubMed: 11677594]

82. Zhao AZ, Huan JN, Gupta S, Pal R, Sahu A. A phosphatidylinositol 3-kinase phosphodiesterase 3B-cyclic AMP pathway in hypothalamic action of leptin on feeding. Nat Neurosci 2002;5:727–728. [PubMed: 12101402]

83. Morrison CD, Morton GJ, Niswender KD, Gelling RW, Schwartz MW. Leptin inhibits hypothalamic Npy and Agrp gene expression via a mechanism that requires phosphatidylinositol 3-OH-kinase signaling. Am J Physiol Endocrinol Metab 2005;289:E1051–E1057. [PubMed: 16046456]

84. Rahmouni K, Haynes WG, Morgan DA, Mark AL. Intracellular mechanisms involved in leptin regulation of sympathetic outflow. Hypertension 2003;41:763–767. [PubMed: 12623993]

85. Bates SH, Stearns WH, Dundon TA, et al. STAT3 signalling is required for leptin regulation of energy balance but not reproduction. Nature 2003;421:856–859. [PubMed: 12594516]

86. Xu AW, Ste-Marie L, Kaelin CB, Barsh GS. Inactivation of signal transducer and activator of transcription 3 in proopiomelanocortin (Pomc) neurons causes decreased pomc expression, mild obesity, and defects in compensatory refeeding. Endocrinology 2007;148:72–80. [PubMed: 17023536]

87. Xue B, Kahn BB. AMPK integrates nutrient and hormonal signals to regulate food intake and energy balance through effects in the hypothalamus and peripheral tissues. J Physiol 2006;574:73–83. [PubMed: 16709629]

88. Minokoshi Y, Alquier T, Furukawa N, et al. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. Nature 2004;428:569–574. [PubMed: 15058305]

89. Lee K, Li B, Xi X, Suh Y, Martin RJ. Role of neuronal energy status in the regulation of adenosine 5′-monophosphate-activated protein kinase, orexigenic neuropeptides expression, and feeding behavior. Endocrinology 2005;146:3–10. [PubMed: 15375032]

90. Andersson U, Filipsson K, Abbott CR, et al. AMP-activated protein kinase plays a role in the control of food intake. J Biol Chem 2004;279:12005–12008. [PubMed: 14742438]Claret M, Smith MA, Batterham RL, et al. AMPK is essential for energy homeostasis regulation and glucose sensing by POMC and AgRP neurons. J Clin Invest 2007;117:2325–2336. [PubMed: 17671657]

91. Cota D, Proulx K, Smith KA, et al. Hypothalamic mTOR signaling regulates food intake. Science 2006;312:927–930. [PubMed: 16690869]

92. Morrison CD, Xi X, White CL, Ye J, Martin RJ. Amino acids inhibit Agrp gene expression via an mTOR-dependent mechanism. Am J Physiol Endocrinol Metab 2007;293:E165–E171. [PubMed: 17374702]

93. Marshall S. Role of insulin, adipocyte hormones, and nutrient-sensing pathways in regulating fuel metabolism and energy homeostasis: a nutritional perspective of diabetes, obesity, and cancer. Sci STKE 2006;2006:re7. [PubMed: 16885148]

94. Rudic RD, McNamara P, Curtis AM, et al. BMAL1 and CLOCK, two essential components of the circadian clock, are involved in glucose homeostasis. PLoS Biol 2004;2:e377. [PubMed: 15523558]

95. Turek FW, Joshu C, Kohsaka A, et al. Obesity and metabolic syndrome in circadian Clock mutant mice. Science 2005;308:1043–1045. [PubMed: 15845877]

96. Ramsey KM, Marcheva B, Kohsaka A, Bass J. The clockwork of metabolism. Annu Rev Nutr 2007;27:219–240. [PubMed: 17430084]

97. Horvath TL. Synaptic plasticity in energy balance regulation. Obesity 2006;14(Suppl 5):228S–233S. [PubMed: 17021372]

98. Horvath TL, Diano S. The floating blueprint of hypothalamic feeding circuits. Nat Rev Neurosci 2004;5:662–667. [PubMed: 15263896]

99. Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. Science 2004;304:108–110. [PubMed: 15064420]

100. Simerly RB. Wired on hormones: endocrine regulation of hypothalamic development. Curr Opin Neurobiol 2005;15:81–85. [PubMed: 15721748]

101. Xu B, Goulding EH, Zang K, et al. Brain-derived neurotrophic factor regulates energy balance downstream of melanocortin-4 receptor. Nat Neurosci 2003;6:736–742. [PubMed: 12796784]

102. Kernie SG, Liebl DJ, Parada LF. BDNF regulates eating behavior and locomotor activity in mice. EMBO J 2000;19:1290–1300. [PubMed: 10716929]

103. Gray J, Yeo GS, Cox JJ, et al. Hyperphagia, severe obesity, impaired cognitive function, and hyperactivity associated with functional loss of one copy of the brain-derived neurotrophic factor (BDNF) gene. Diabetes 2006;55:3366–3371. [PubMed: 17130481]

104. Gray J, Yeo G, Hung C, et al. Functional characterization of human NTRK2 mutations identified in patients with severe early-onset obesity. Int J Obes 2007;31:359–364.

105. Wang C, Bomberg E, Billington C, Levine A, Kotz CM. Brain-derived neurotrophic factor in the hypothalamic paraventricular nucleus increases energy expenditure by elevating metabolic rate. Am J Physiol Regul Integr Comp Physiol 2007;293:R992–R1002. [PubMed: 17567712]

106. Pelleymounter MA, Cullen MJ, Wellman CL. Characteristics of BDNF-induced weight loss. Exp Neurol 1995;131:229–238. [PubMed: 7534721]

107. Diano S, Farr SA, Benoit SC, et al. Ghrelin controls hippocampal spine synapse density and memory performance. Nat Neurosci 2006;9:381–388. [PubMed: 16491079]

108. Schmid DA, Held K, ng M, et al. Ghrelin stimulates appetite, imagination of food, GH, ACTH, and cortisol, but does not affect leptin in normal controls. Neuropsychopharmacology 2005;30:1187–1192. [PubMed: 15688086]

109. Wortley KE, del Rincon JP, Murray JD, et al. Absence of ghrelin protects against early-onset obesity. J Clin Invest 2005;115:3573–3578. [PubMed: 16322795]

110. Zigman JM, Nakano Y, Coppari R, et al. Mice lacking ghrelin receptors resist the development of diet-induced obesity. J Clin Invest 2005;115:3564–3572. [PubMed: 16322794]

111. Sakkou M, Wiedmer P, Anlag K, et al. A role for brain-specific homeobox factor bsx in the control of hyperphagia and locomotory behavior. Cell Metab 2007;5:450–463. [PubMed: 17550780]

112. Apelbaum AF, Perrut A, Chaput M. Orexin A effects on the olfactory bulb spontaneous activity and odor responsiveness in freely breathing rats. Regul Pept 2005;129:49–61. [PubMed: 15927698]

113. Hardy AB, Aioun J, Baly C, et al. Orexin A modulates mitral cell activity in the rat olfactory bulb: patch-clamp study on slices and immunocytochemical localization of orexin receptors. Endocrinology 2005;146:4042–4053. [PubMed: 15976062]

114. Julliard AK, Chaput MA, Apelbaum A, et al. Changes in rat olfactory detection performance induced by orexin and leptin mimicking fasting and satiation. Behav Brain Res 2007;183:123–129. [PubMed: 17624453]

115. Getchell TV, Kwong K, Saunders CP, Stromberg AJ, Getchell ML. Leptin regulates olfactory-mediated behavior in ob/ob mice. Physiol Behav 2006;87:848–856. [PubMed: 16549076]

116. Elias CF, Aschkenasi C, Lee C, et al. Leptin differentially regulates NPY and POMC neurons projecting to the lateral hypothalamic area. Neuron 1999;23:775–786. [PubMed: 10482243]

117. Elias CF, Saper CB, Maratos-Flier E, et al. Chemically defined projections linking the mediobasal hypothalamus and the lateral hypothalamic area. J Comp Neurol 1998;402:442–459. [PubMed: 9862320]

118. Kotz CM. Integration of feeding and spontaneous physical activity: role for orexin. Physiol Behav 2006;88:294–301. [PubMed: 16787655]

119. Thorpe AJ, Teske JA, Kotz CM. Orexin A-induced feeding is augmented by caloric challenge. Am J Physiol Regul Integr Comp Physiol 2005;289:R367–R372. [PubMed: 15947069]

120. Rodgers RJ, Ishii Y, Halford JC, Blundell JE. Orexins and appetite regulation. Neuropeptides 2002;36:303–325. [PubMed: 12450737]

121. Zhang M, Kelley AE. Enhanced intake of high-fat food following striatal mu-opioid stimulation: microinjection mapping and fos expression. Neuroscience 2000;99:267–277. [PubMed: 10938432]

122. Kelley AE, Bakshi VP, Haber SN, et al. Opioid modulation of taste hedonics within the ventral striatum. Physiol Behav 2002;76:365–377. [PubMed: 12117573]

123. Will MJ, Franzblau EB, Kelley AE. Nucleus accumbens mu-opioids regulate intake of a high-fat diet via activation of a distributed brain network. J Neurosci 2003;23:2882–2888. [PubMed: 12684475]

124. Kelley AE, Bless EP, Swanson CJ. Investigation of the effects of opiate antagonists infused into the nucleus accumbens on feeding and sucrose drinking in rats. J Pharmacol Exp Ther 1996;278:1499–1507. [PubMed: 8819538]

125. Kringelbach ML. Food for thought: hedonic experience beyond homeostasis in the human brain. Neuroscience 2004;126:807–819. [PubMed: 15207316]

126. Berridge KC, Robinson TE. Parsing reward. Trends Neurosci 2003;26:507–513. [PubMed: 12948663]

127. Berridge KC. Food reward: brain substrates of wanting and liking. Neurosci Biobehav Rev 1996;20:1–25. [PubMed: 8622814]

128. Dayan P, Balleine BW. Reward, motivation, and reinforcement learning. Neuron 2002;36:285–298. [PubMed: 12383782]

129. Wyvell CL, Berridge KC. Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward “wanting” without enhanced “liking” or response reinforcement. J Neurosci 2000;20:8122–8130. [PubMed: 11050134]

130. Kaczmarek HJ, Kiefer SW. Microinjections of dopaminergic agents in the nucleus accumbens affect ethanol consumption but not palatability. Pharmacol Biochem Behav 2000;66:307–312. [PubMed: 10880683]

131. Pecina S, Cagniard B, Berridge KC, Aldridge JW, Zhuang X. Hyperdopaminergic mutant mice have higher “wanting” but not “liking” for sweet rewards. J Neurosci 2003;23:9395–9402. [PubMed: 14561867]

132. Cannon CM, Palmiter RD. Reward without dopamine. J Neurosci 2003;23:10827–10831. [PubMed: 14645475]

133. Wyvell CL, Berridge KC. Incentive sensitization by previous amphetamine exposure: increased cue-triggered “wanting” for sucrose reward. J Neurosci 2001;21:7831–7840. [PubMed: 11567074]

134. Berridge KC, Valenstein ES. What psychological process mediates feeding evoked by electrical stimulation of the lateral hypothalamus? Behav Neurosci 1991;105:3–14. [PubMed: 2025391]

135. Figlewicz DP. Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. Am J Physiol Regul Integr Comp Physiol 2003;284:R882–R892. [PubMed: 12626355]

136. Hommel JD, Trinko R, Sears RM, et al. Leptin receptor signaling in midbrain dopamine neurons regulates feeding. Neuron 2006;51:801–810. [PubMed: 16982424]

137. Fulton S, Pissios P, Manchon RP, et al. Leptin regulation of the mesoaccumbens dopamine pathway. Neuron 2006;51:811–822. [PubMed: 16982425]

138. Farooqi IS, Bullmore E, Keogh J, et al. Leptin regulates striatal regions and human eating behavior. Science 2007;317:1355. [PubMed: 17690262]

139. Abizaid A, Liu ZW, Andrews ZB, et al. Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. J Clin Invest 2006;116:3229–3239. [PubMed: 17060947]
140. Jerlhag E, Egecioglu E, Dickson SL, et al. Ghrelin administration into tegmental areas stimulates locomotor activity and increases extracellular concentration of dopamine in the nucleus accumbens. Addict Biol 2007;12:6–16. [PubMed: 17407492]
141. Balleine BW. The neural basis of choice and decision making. J Neurosci 2007;27:8159–8160.
142. Murray EA, O'Doherty JP, Schoenbaum G. What we know and do not know about the functions of the orbitofrontal cortex after 20 years of cross-species studies. J Neurosci 2007;27:8166–8169. [PubMed: 17670960]
143. Alonso-Alonso M, Pascual-Leone A. The right brain hypothesis for obesity. JAMA 2007;297:1819–1822. [PubMed: 17456824]
144. Regard M, Landis T. "Gourmand syndrome": eating passion associated with right anterior lesions. Neurology 1997;48:1185–1190. [PubMed: 9153440]
145. Uher R, Treasure J. Brain lesions and eating disorders. J Neurol Neurosurg Psychiatry 2005;76:852–857. [PubMed: 15897510]
146. Craig AD. Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol 2003;13:500–505. [PubMed: 12965300]
147. Craig AD. Forebrain emotional asymmetry: a neuroanatomical basis? Trends Cogn Sci 2005;9:566–571. [PubMed: 16275155]
149. DelParigi A, Chen K, Salbe AD, et al. Successful dieters have increased neural activity in cortical areas involved in the control of behavior. Int J Obes 2007;31:440–448.
150. Le DS, Pannacciulli N, Chen K, et al. Less activation of the left dorsolateral prefrontal cortex in response to a meal: a feature of obesity. Am J Clin Nutr 2006;84:725–731. [PubMed: 17023697]
151. Miller JL, James GA, Goldstone AP, et al. Enhanced activation of reward mediating prefrontal regions in response to food stimuli in Prader-Willi syndrome. J Neurol Neurosurg Psychiatry 2007;78:615–619. [PubMed: 17158560]
152. Petrovich GD, Ross CA, Holland PC, Gallagher M. Medial prefrontal cortex is necessary for an appetitive contextual conditioned stimulus to promote eating in sated rats. J Neurosci 2007;27:6436–6441. [PubMed: 17567804]
153. Levine JA, Eberhardt NL, Jensen MD. Leptin responses to overfeeding: relationship with body fat and nonexercise activity thermogenesis. J Clin Endocrinol Metab 1999;84:2751–2754. [PubMed: 10443673]
154. Castaneda TR, Jurgens H, Wiedmer P, et al. Obesity and the neuroendocrine control of energy homeostasis: the role of spontaneous locomotor activity. J Nutr 2005;135:1314–1319. [PubMed: 15867332]
155. Anderson JW, Konz EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nut 2001;74:579–584.
156. Vella KR, Burnside AS, Brennan KM, Good DJ. Expression of the hypothalamic transcription factor Nhlh2 is dependent on energy availability. J Neuroendocrinol 2007;19:499–510. [PubMed: 17532796]
157. Coyle CA, Jing E, Hosmer T, et al. Reduced voluntary activity precedes adult-onset obesity in Nhlh2 knockout mice. Physiol Behav 2002;77:387–402. [PubMed: 12419415]
158. Kristensen P, Judge ME, Thim L, et al. Hypothalamic CART is a new anorectic peptide regulated by leptin. Nature 1998;393:72–76. [PubMed: 9590691]
159. Kimmel HL, Thim L, Kuhar MJ. Activity of various CART peptides in changing locomotor activity in the rat. Neuropeptides 2002;36:9–12. [PubMed: 12147209]
160. Hwa JJ, Ghibaudi L, Gao J, Parker EM. Central melanocortin system modulates energy intake and expenditure of obese and lean Zucker rats. Am J Physiol Regul Integr Comp Physiol 2001;281:R444–R451. [PubMed: 11448846]
161. Adage T, Scheurink AJ, de Boer SF, et al. Hypothalamic, metabolic, and behavioral responses to pharmacological inhibition of CNS melanocortin signaling in rats. J Neurosci 2001;21:3639–3645. [PubMed: 11331393]

162. Moffett M, Stanek L, Harley J, et al. Studies of cocaine- and amphetamine-regulated transcript (CART) knockout mice. Peptides 2006;27:2037–2045. [PubMed: 16762458]

163. Ste Marie L, Miura GI, Marsh DJ, Yagaloff K, Palmiter RD. A metabolic defect promotes obesity in mice lacking melanocortin-4 receptors. Proc Natl Acad Sci USA 2000;97:12339–12344. [PubMed: 11027312]

164. Bi S, Scott KA, Hyun J, Ladenheim EE, Moran TH. Running wheel activity prevents hyperphagia and obesity in Otsuka long-evans Tokushima Fatty rats: role of hypothalamic signaling. Endocrinology 2005;146:1676–1685. [PubMed: 15625240]

165. Novak CM, Kotz CM, Levine JA. Central orexin sensitivity, physical activity, and obesity in diet-induced obese and diet-resistant rats. Am J Physiol Endocrinol Metab 2006;290:E396–E403. [PubMed: 16188908]

166. Teske JA, Levine AS, Kuskowski M, Levine JA, Kotz CM. Elevated hypothalamic orexin signaling, sensitivity to orexin A, and spontaneous physical activity in obesity-resistant rats. Am J Physiol Regul Integr Comp Physiol 2006;291:R889–R899. [PubMed: 16763079]

167. Thorpe AJ, Kotz CM. Orexin A in the nucleus accumbens stimulates feeding and locomotor activity. Brain Res 2005;1050:156. [PubMed: 15979595]

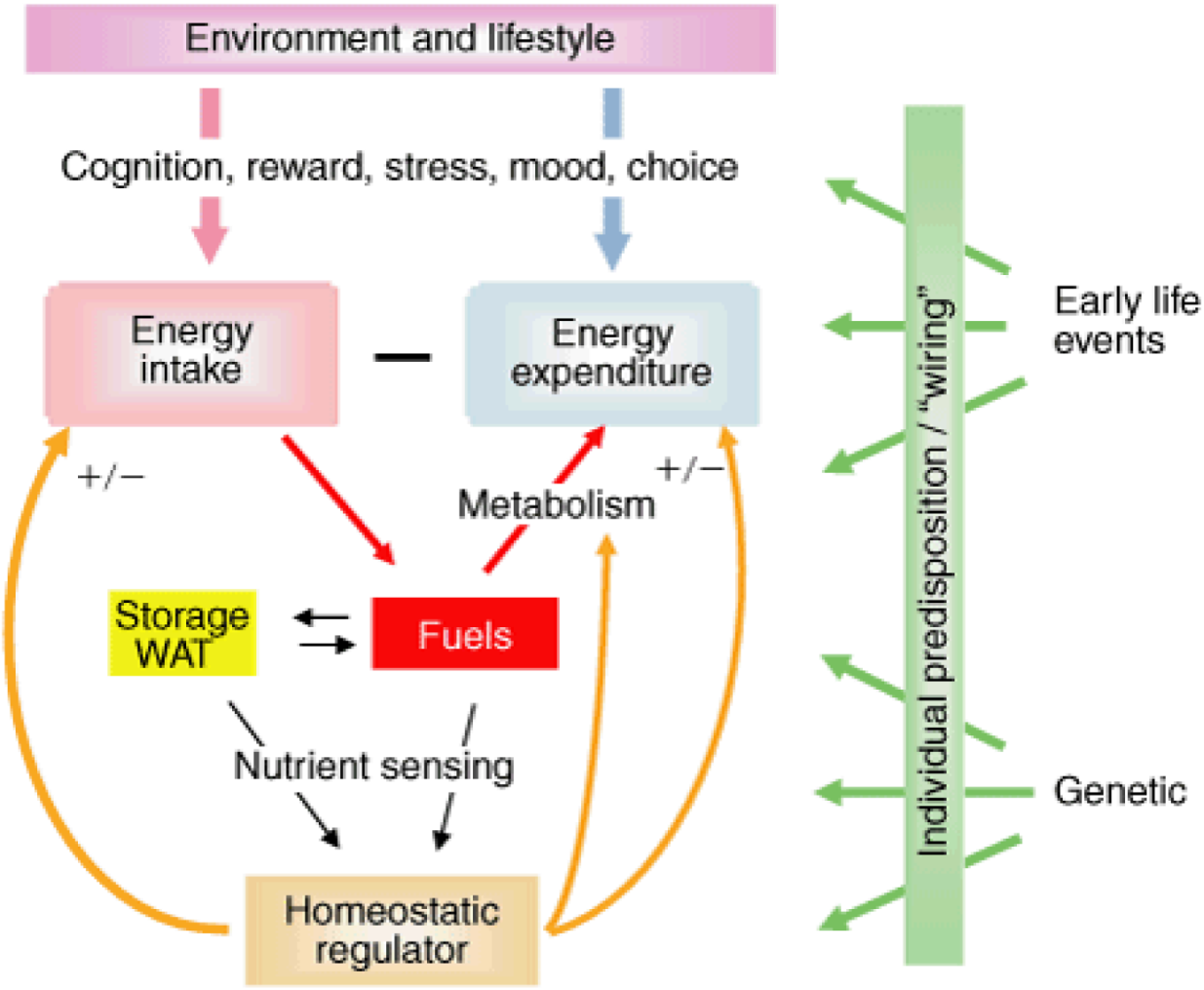


**Figure 1.**
Major mechanisms and factors determining energy balance.

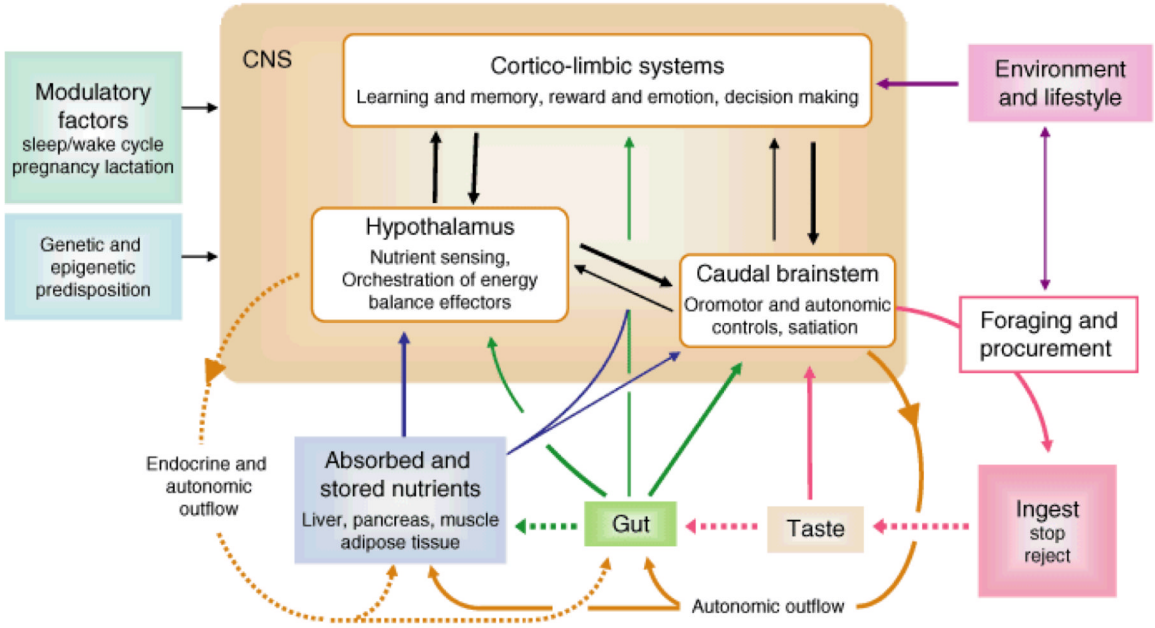


**Figure 2.**

Highly schematic diagram showing major components and flow of information of the peripheral and central systems involved in energy balance, regulation, and control of food intake. CNS, central nervous system.

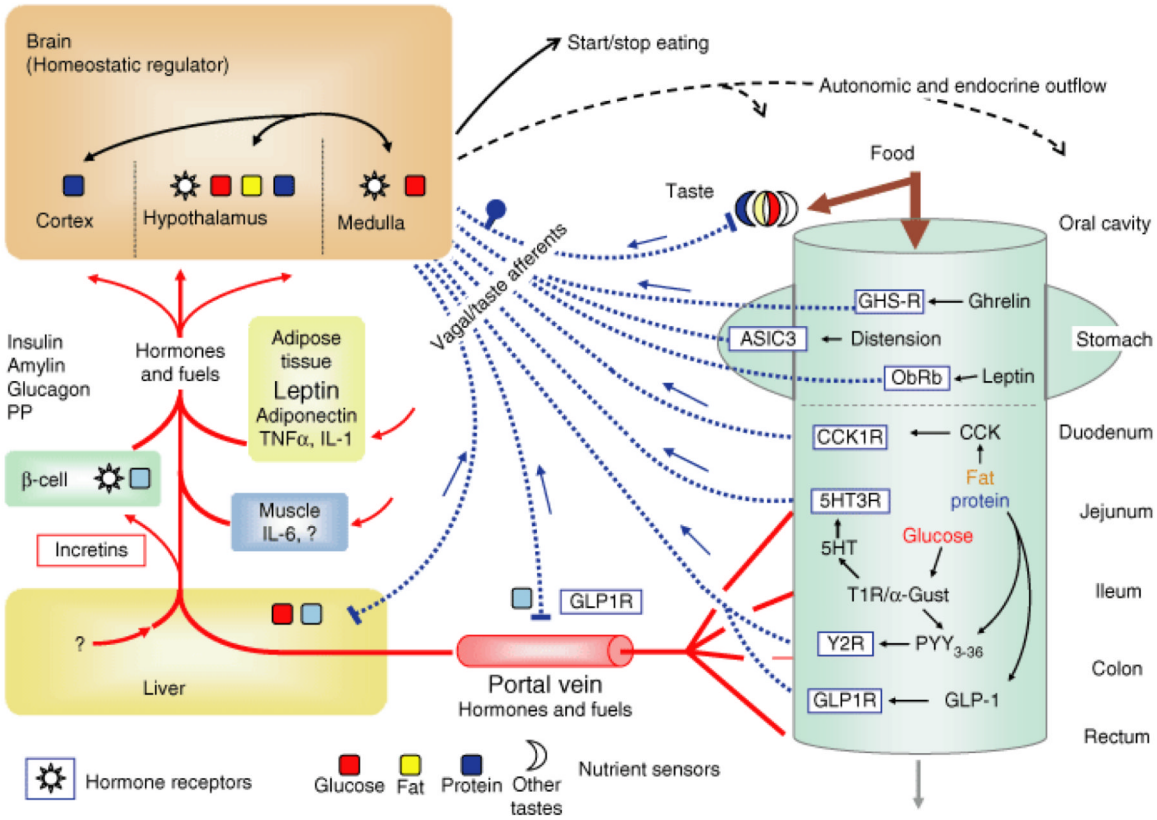


**Figure 3.**

Nutrient sensing in the alimentary canal and the control of food intake. Simplified schematic diagram showing the major pre- and postabsorptive transduction sites and mechanisms for the detection of ingested food and its macronutrient components. Nutrient information is sent to the brain through vagal and taste afferents (heavy dotted lines) or through the blood circulation (full lines). Specific receptors expressed by vagal afferent neurons are shown in rectangular boxes. Specific sensor mechanisms demonstrated for glucose, amino acids/proteins, and lipids/fatty acids are shown by gray, striped, and white squares, respectively. CCK, cholecystokinin; GHS-R, ghrelin receptor; GLP-1, glucagon-like peptide-1; IL-1, interleukin-1; PYY, peptide YY; TNF-α, tumor necrosis factor-α.

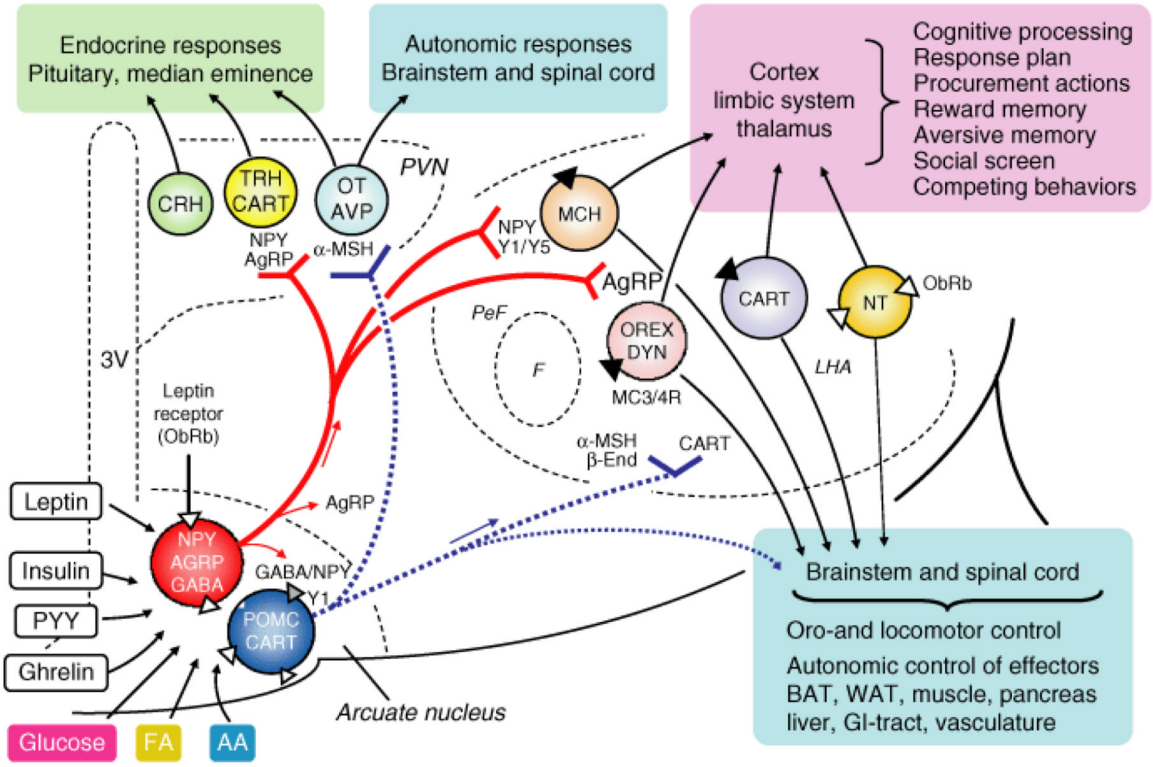


**Figure 4.**

Hypothalamic peptidergic circuitry related to feeding and energy balance. Highly simplified diagram showing the two known neuron populations in the arcuate nucleus sensitive to signals of fuel availability and their projections to other key neuron populations orchestrating the adaptive behavioral, autonomic, and endocrine responses. CART, cocaine- and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; GABA, γ-aminobutyric acid; MCH, melanin concentrating hormone; α-MSH, α-melanocyte-stimulating hormone; PVN, paraventricular nucleus.

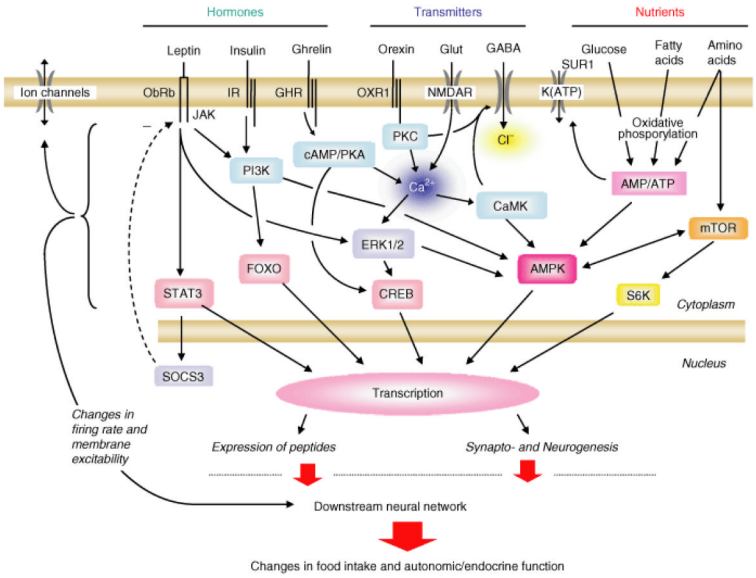


**Figure 5.**

Molecular mechanisms of integration of various signals by hypothetical “nutrient-sensing neurons” in the mediobasal hypothalamus. AMPK, adenosine monophosphate-activated kinase; ATP, adenosine triphosphate; GABA, γ-aminobutyric acid; mTOR, mammalian target of rapamycin.

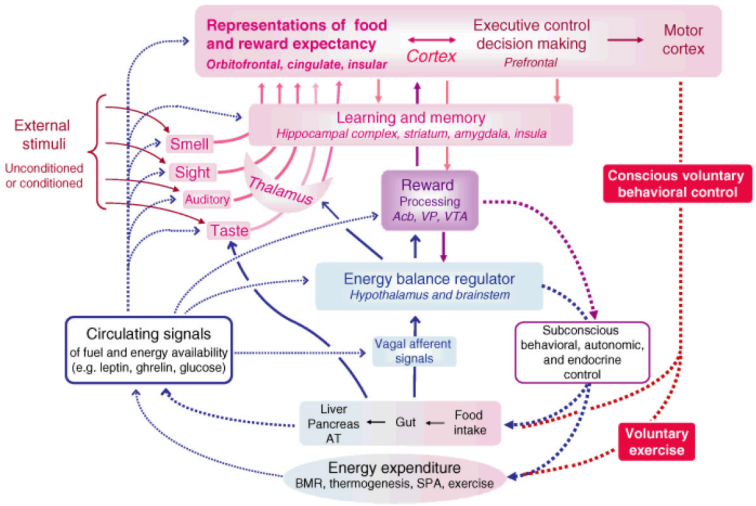


**Figure 6.**

Highly simplified schematic diagram showing the multiple neural systems and pathways controlling food intake, energy expenditure, and energy balance, with emphasis on interactions between “metabolic,” “cognitive,” and “rewarding” brain systems.