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Regulation of Energy Balance and Body Weight by the Brain: A Distributed System Prone to Disruption

Lucy F. Faulconbridge[1] and **Matthew R. Hayes**[2]

[1]Center for Weight and Eating Disorders, Department of Psychiatry, University of Pennsylvania, School of Medicine, 3535 Market Street, Philadelphia, PA 19104

[2]Translational Neuroscience Program, Department of Psychiatry, University of Pennsylvania, TRL Building, 125 South 31st Street, Philadelphia, PA 19104

Synopsis

The central nervous system control of energy balance is a multi-determined process involving a distributed and redundant network of communication that exists between various brain regions and the body. The brain continuously receives, processes, and issues autonomic and behavioral output commands to respond to internal signals of energy availability. These signals are communicated to the brain either through a humoral pathway via the circulatory system, or through neuronal communication via the vagus and spinal nerves. Environmental, emotional, rewarding, and learned factors influence the brain's perception of these internal signals and ultimately promote behaviors that drive the system to conserve energy and ingest energy-dense foods in excess. Therefore, this review discusses the energy balance system under normal physiological conditions, as well as the processes that have evolutionarily developed to promote energy surplus.

Energy balance refers to the physiological mechanisms that are reciprocally linked to ensure that adequate energy is available for cellular processes required for survival and reproduction. As the term implies, there are two arms of this balance, each equally important in maintaining energy homeostasis: energy intake (i.e., food intake) and energy expenditure (e.g., physical activity, metabolism, and core body temperature regulation). Any internal or external perturbations to the physiological mechanisms governing either energy intake or expenditure will almost undoubtedly affect the other arm of the system and result in a disruption in the energy balance system as a whole. The coordinated regulation of energy balance is therefore ultimately controlled by the central nervous system (CNS). Given the reciprocal link between energy intake and expenditure, and the fundamental requirement to maintain adequate energy for survival and reproduction, the CNS control of energy balance is one that is multi-determined. Multiple internal signals, neural receptors, and regions of the brain operate with a degree of redundancy to ensure that enough energy exists to sustain life. This review will discuss some of the classic internal signals, physiological mechanisms, the distinct nuclei within the brain, as well as the brain's response to environmental stimuli, that together play an essential role in energy balance regulation.

All correspondence to: Lucy F. Faulconbridge, Ph.D., lucyhf@mail.med.upenn.edu, T: 215-746-7191, F: 215-898-2878 and Matthew R. Hayes, Ph.D., hayesmr@sas.upenn.edu, T: 215-573-6070, F: 215-898-9439.

CNS control of food intake

When discussing how the brain regulates energy intake, we must consider "the meal" as the fundamental unit of energy intake.[1] Thus, the physiological systems that exist to regulate food intake function to negatively or positively influence food intake either during a meal (within-meal) and/or between a meal, influencing the time between meals and the frequency of meal taking (inter-meal-interval).[1–4] Once a meal has begun, and the ingested food enters the oral cavity, the brain perceives various components of the meal including the taste and texture of the food, potentially communicating the presence of preferred energy-rich nutrients (e.g., fats and sugars) that promote for further feeding.[5–7] As food is swallowed and enters into the gastrointestinal (GI) tract, information about the volume of the ingested food through the mechanical distension of the stomach is relayed to the brain. In turn, these gastric-inhibitory signals begin to counteract the positive meal-promoting signals from the oral cavity. In addition, the various chemical and nutritive properties of the food also give rise to the release of a number of gut peptides (hormones) and neurotransmitters from the GI tract that communicate to the brain about the ongoing status of the meal. The majority of these signals are referred to as *satiation signals*, or within-meal intake inhibitory signals.[1] As these satiation signals accumulate, feeding rate slows and eventually *satiety*, or meal termination, is achieved. Satiety then persists from the end of one meal to the start of the next meal.

To date, an extensive number of GI-derived satiation signals have been identified (some are discussed in more detail below), each with a rich literature base unto themselves. A short, non-comprehensive list of some of the classic satiation signals includes: cholecystokinin (CCK); serotonin (5-HT); peptide-YY (PYY); glutamate; enterostatin; glucagon-like-peptide-1 (GLP-1); and gastric distension. While specific receptor populations exist within the CNS for many of these GI-derived satiation signals, under normal physiological conditions, the available circulating levels of these gut-peptides and neurotransmitters are not elevated in sufficient quantity to have direct action within the brain.[4, 8] Instead, the majority of GI-derived satiation signaling is communicated to the brain via afferent fibers of the vagus nerve (cranial nerve X), which innervates all of the organs within the peritoneal and thoracic cavity.[4, 8, 9] Thus, the presence of food within the lumen of the GI tract results in the release of the aforementioned gut-peptides, which in turn activate specific receptors expressed on the dendritic terminals of vagal afferents that innervate the GI tract. This vagal afferent activation is then relayed to the brainstem where processing of the inhibitory signals begins. The vagal communication and CNS processing of these signals will be discussed in greater detail below.

The physiological control of meal taking is not only governed by GI-derived vagally-mediated satiation signals. The brain also detects a number of circulating hormones and nutrients (e.g., glucose, free-fatty acids) that communicate the availability of circulating and stored energy. These circulating hormones have been previously termed, "long-term energy status signals" or "adiposity signals" [2, 10] and include neuropeptides released from the pancreas (e.g., insulin, glucagon, amylin), adipose tissue (e.g., leptin, adiponectin), as well as the GI tract (e.g., ghrelin). While receptors for many of these signals exist on the vagus nerve, the principal pathway of communication for these long-term energy status signals is one of an endocrine-pathway with direct brain activation. In other words, they circulate in the blood, cross the blood brain barrier, and act directly on receptors in the brain.

CNS processing of gut-peptide satiation and energy-status hormonal signals

Historically, much of the field's attention has focused on the role of hypothalamic nuclei in regulating energy balance. While this hypothalamic-centric work greatly added to our knowledge of the neural control circuitry and intracellular signaling pathways meditating food intake and energy expenditure control,[10–13] it neglected the role of other important brain structures involved in energy balance regulation. Only within the last decade has the field at large started to embrace the perspective that the CNS regulation of energy balance involves a multitude of distributed nuclei that each has a critical role in energy balance regulation.[2, 14–19] Reciprocal ascending and descending projections exist between many brain structures to control food intake, as well as energy expenditure. Many of the previously described vagally-mediated satiation signals, as well as the circulating energy-status signals, engage processing of the same brain structures and subsequently influence not only ingestive behavior but energy expenditure autonomic responses (e.g., heart rate, core body temperature, nutrient metabolism and storage).[2, 9, 16, 20]

Among the CNS nuclei controlling energy balance, the more evolutionarily conserved nuclei of the caudal brainstem and hypothalamus are often considered regulatory centers of energy balance from a *homeostatic* (energy need-based) perspective. However, metabolic need (i.e., when the body is in a state of negative energy balance) is not the only motivation to consume food. Other factors influencing food intake include the rewarding features of the food, temporal factors (time of day, season), emotion, and cognition (learning, memory, social cues). Collectively, these factors influence the *non-homeostatic/hedonic* control of food intake and could be discussed with extensive detail in numerous reviews. The hedonic control centers of energy intake are often classified as higher-order nuclei and include, but are not limited to, the hippocampus, amygdala, ventral tegmental area (VTA), nucleus accumbens (NAc) and prefrontal cortex. Figure 1 attempts to illustrate: 1) the distributed CNS nuclei controlling energy intake; and 2) the perspective that circulating energy-status signals, as well as vagally-mediated satiation signals, can act either directly or indirectly on both homeostatic nuclei (hypothalamus and nucleus tractus solitarius [NTS] in the brainstem) and hedonic/non-homeostatic nuclei. Signals considered relevant to homeostatic control of feeding may also affect neural circuitries associated with hedonic feeding, suggesting that the functional descriptors to brain regions as "homeostatic" vs. "hedonic" may be too restrictive, as individual brain regions contribute to both homeostatic and non-homeostatic control functions.[16, 21]

Satiation and long-term energy status signals

The rewarding properties of food, together with the hedonic processes listed above, and described in more detail below, contribute to the cognitive decision to procure food and initiate feeding. However, it is very clear that the determinants which initiate a meal are not purely appetitive in nature, but also involve internal hunger cues. While orexigenic (i.e., hunger/meal-initiating) hormonal signals do exist (e.g., ghrelin) and contribute to overall food intake regulation, the vast majority of evidence suggests that the sensation of hunger occurs in response to 1) the accumulation of these orexigenic signals, 2) the decrease in anorectic satiation signals from the last meal[1, 4] and, 3) the decrease in specific energy-status signals (e.g., leptin).[2] Following digestion, the decrease or absence of nutrient content within the GI tract results in a decrease or cessation of hormonal gut-peptide release from the GI tract. Thus, the satiation gut peptides not only negatively communicate to the brain during a meal, eventually leading to satiety, but the lack of signaling by these hormones can actually promote meal initiation (as a result of an absence in the vagally-mediated inhibitory signal). Among the plethora of GI- derived satiation signals that could be discussed, two hormones

have received the most attention over the last four decades for their intake-inhibitory role: CCK and GLP-1. Each is discussed in very brief detail below and in much greater detail by others.[3, 4, 17, 22–24] Likewise, among a wide variety of circulating energy-status signals that contribute to energy balance control, leptin and ghrelin have perhaps been investigated more than others[2, 15, 25–27] and are also briefly discussed.

Cholecystokinin (CCK)

Gibbs, Young and Smith first reported in 1973 that exogenous administration of CCK produces a dose-dependent decrease in meal size.[28] A number of studies have since revealed that CCK (released from intestinal "I" cells in response to ingestion of nutrients[29, 30]) is one of the most biologically potent satiety peptides. Systemic CCK acts via CCK-1 receptors, found densely distributed in the periphery on the vagus nerve and in select regions of the CNS.[31, 32] CCK-induced suppression of intake is enhanced when combined with other GI-derived satiation signals, such as serotonin[33–37] or gastric distension.[38, 39] Recent evidence also suggests that in addition to the traditional role of CCK as a within-meal inhibitory signal, CCK may interact with specific long-term energy status signals, such as insulin or leptin,[2, 18, 40–42] demonstrating a role for CCK not only in the control of meal size, but also in long-term body weight regulation and overall energy homeostasis.

Glucagon-like-peptide-1 (GLP-1)

GLP-1 is a neuropeptide that is endogenously released, principally from two distinct sources within the body: 1) "L" cells in the GI tract following ingestion of food;[43–45] and 2) neurons of the nucleus NTS in the caudal brainstem that project to GLP-1 receptors (GLP-1R), both locally and throughout the brain.[46–48] Exogenous stimulation of either peripheral or central GLP-1Rs results in reduced food intake,[49–53] inhibition of gastric emptying,[49, 54] and increased glucose-stimulated insulin secretion.[55–57] Within the periphery, GLP-1 activates GLP-1R on vagal afferent neurons in the small intestine, portal vein, liver and upper GI tract. GLP-1 afferent signals are processed by CNS neurons which then drive neuroendocrine, behavioral, and physiological responses that result in improved glycemic control and reduced feeding. One such neuroendocrine response to vagal afferent activation by GLP-1 is the subsequent vagal efferent neural transmission to the pancreatic β-cell, resulting in insulin secretion.[22, 58, 59]

The effects of GLP-1 in inhibiting food intake and regulating blood glucose/insulin levels have led to two separate emerging pharmacological approaches in an effort to take advantage of the peripheral GLP-1 system to treat type 2 diabetes mellitus (T2DM) and potentially obesity: 1) development of long-lasting GLP-1R analogues (e.g., exendin-4 [Byetta], liraglutide [Victoza]), and 2), dipeptidyl peptidase IV (DPP-IV) (an enzyme that degrades GLP-1) inhibitors (e.g., sitagliptin [Januvia]), which elevate endogenous GLP-1 levels. Both of these clinical strategies are FDA-approved for the treatment of T2DM for improving blood glucose regulation. Preliminary evidence also suggests that long-acting GLP-1R agonists (liraglutide and exendin-4) may also produce weight loss as a consequence of reduced food intake.[60–63]

Leptin

Discovery of the adipose tissue-derived hormone leptin[64] has transformed our understanding of the function of white adipose tissue from one of a simple energy storage depot to the view that adipose tissue is an active endocrine organ. Thus, the greater the stores of energy in the adipose tissue (i.e., the greater the fat mass of an individual), the larger the available circulating levels of leptin. We now appreciate that leptin acting on its receptors (LepRb a.k.a. ObRb) in the brain contributes significantly to the control of feeding and energy expenditure.[2, 10, 15, 18, 25] Under normal physiological conditions in a lean human or animal,

both the total amount of adiposity, and fluctuation in adiposity levels, is minimal. Under these conditions slight variations in circulating leptin levels, communicating energy storage within the adipose tissue, are sensed by the brain, and appropriate CNS signaling pathways are engaged to either increase or decrease food intake and energy expenditure to normalize energy need. Unfortunately though, in the case of energy surplus (i.e., obesity), leptin levels are chronically elevated, and the brain fails to correctly perceive and respond to the over accumulation of the leptin signal. Such a response is known as "leptin resistance," [25, 65] discussed in more detail below.

Ghrelin

Ghrelin is a peptide hormone released in the stomach and small intestines,[66, 67] and is the only known peripheral peptide to increase food intake. (All other peripheral feeding-related signals act to terminate meals.) Ghrelin binds to the growth hormone secretatogue receptor (GHS-R) located in both orexigenic regions (such as the hypothalamus and caudal brainstem[68, 69]) and hedonic brain regions (such as the VTA[70]). Exogenous ghrelin administration to rodents or humans results in potent increases in hunger, food intake, and body weight.[71, 72] Studies in rodents suggest that ghrelin augments food intake by increasing primarily the frequency of meals, with smaller effects on meal size.[73] The notion of ghrelin as a physiological hunger signal is supported by the dramatic increase in plasma ghrelin levels observed before meals, and their rapid decline following food consumption.[71,74] Work to develop ghrelin antagonists and mimetics to interfere with the perception of hunger by the elevation in this hormone is underway as a potential therapeutic tool for obesity, although this work has been largely unsuccessful thus far.

A modern environment disrupts biology

The neural control of energy balance is tightly regulated, utilizing an array of internal signals to defend body weight, such that small perturbations in the energy status of the body are detected rapidly and remedied. Yet despite such tight regulation, the system is vulnerable to disruption by environmental manipulations. The areas of the brain controlling the regulation of food intake evolved at a time when food sources were scarce and large amounts of physical activity were required to obtain enough calories for survival. The resulting "thrifty genotype,"[75] which allowed for easy storage of fat, conferred an obvious advantage on the survival of humans and their young. Now however, this genotype operates in a modern world that is exposed to a "toxic environment," [76] characterized by the increased availability of cheap, energy-dense foods and a decreased need for physical activity. As such, the neurochemical signals that have evolved to initiate or terminate feeding are no match for the ever-present array of highly palatable, calorically-rich foods that are readily available in the environment. As Egger and Swinburn (1997) suggest, obesity is "a normal response to an abnormal environment" (p. 477).[77]

Leptin and insulin resistance

Under conditions in which the body is challenged by a constant over-supply of nutrients, the normal functioning of the physiological mechanisms maintaining energy balance is disrupted. A state of chronic nutrient excess (caused by over-consumption of calorically-dense foods) leads eventually to a blunting of signaling in the insulin and leptin pathways, a concept referred to as "resistance." As described above, under normal conditions, elevated leptin levels act centrally to decrease feeding and prevent obesity. Likewise insulin, in the non-obese state, acts on peripheral cells (e.g., skeletal muscle) to enhance utilization of blood glucose. Under conditions of excess (i.e., obesity), even though large amounts of leptin and insulin circulate in the blood, there are disruptions in the receptor and intracellular signaling responses for these hormones. In short, the over-saturation of the hormone at the

receptor decreases the receptor response to the hormone, such that leptin fails to suppress food intake and increase energy expenditure. Thus, weight gain continues, further exacerbating the obesity phenotype. Likewise, insulin signaling is blunted in the obese state, such that cells do not effectively utilize the excessive circulating levels of glucose. A vicious cycle develops, such that a person already consuming too many calories now has less sensitivity to the normal neurochemical signals that should be leading to meal termination. Over time this resistance to leptin and insulin signaling further predisposes the individual towards T2DM and obesity.

Our Love of Highly Palatable Foods

Our understanding of humans' preference for highly palatable foods (those typically high in fat and sugar), even in the absence of hunger, has improved over the last decade. It is now clear that two complementary neural systems regulate food intake: homeostatic and hedonic circuits.[78, 79] As discussed above, homeostatic circuits refer to pathways that alter the motivation to eat based on the energy status of the body. Key homeostatic brain areas that integrate neural and peripheral signals are the hypothalamus and caudal brainstem.[5, 80–82] In contrast, hedonic neural circuits control the rewarding properties of food. Neural areas implicated include the mesolimbic dopamine system (including the striatum and VTA), the orbitofrontal cortex (OFC), and the amygdala.[83–87] These circuits, which also mediate the rewarding response to drugs of abuse, make highly palatable foods attractive even in the absence of caloric/nutritional deficiency.[79, 88]

Substances that are hedonically pleasing, such as food, sex and drugs of abuse, stimulate dopamine release from neurons in the VTA that project to the nucleus accumbens (NAc; also known as the ventral striatum). [6, 89, 90] This increased release of dopamine may help to coordinate an organism's attempts to obtain food through increased arousal, psychomotor activation, and increased memory for food-related stimuli.[91] The mechanism by which food intake increases dopamine signaling is not yet clear, although there are bi-directional neuronal projections between the VTA/NAc and several of the hypothalamic nuclei involved in homeostatic regulation.[92–94] Thus, while hedonic and homeostatic pathways frequently work in synergy to control food intake, the hedonic circuit may override homeostatic pathways in the fed state by increasing the desire to ingest foods that are highly palatable.[95]

Neural mediation of food in the human brain

Several recent imaging studies in humans have examined activity in homeostatic and hedonic areas of the brain in order to better understand why some people do not stop eating, even when satiated. The studies examine neural activation in response to participants merely seeing pictures of food (i.e., food cues), or to actually ingesting various food items.

Response to food cues

Typically, these investigations have used either PET or fMRI to compare responses to non-food vs. food images, or responses to high- vs. low-calorie (or palatability) food images.[96, 97] In lean individuals, food cues (and high-calorie food cues in particular) consistently evoke activation in hedonic pathways, including the VTA, NAc and OFC cortex.[98, 99] Interestingly, obese individuals appear to show a greater response to food cues in these areas compared to their lean counterparts.[100, 101] These findings present the possibility that obese individuals anticipate greater hedonic reward from eating, and that appetitive food cues may stimulate greater appetitive drive in heavier individuals.

Response to feeding

Several studies have investigated the neural response to glucose ingestion[102–104] or to calorie-dense preferred foods such as chocolate,[99] and found correlations between regional cerebral blood flow and satiety. Gautier and colleagues investigated differences in neural activation in response to a mixed nutrient meal between lean and obese men[105] and women[106] using PET and the tracer [^{15}O] labeled water. Increases in regional cerebral blood flow were found in the prefrontal and occipital cortex (hedonic areas); decreases were observed in the insular cortex, limbic and paralimbic regions, and the hypothalamus. This pattern is consistent with previous findings.[107] Gautier et al. hypothesized that the hypothalamus, insula, and limbic/paralimbic regions make up a central orexigenic network (including both homeostatic and hedonic components). This network receives inhibitory projections from the prefrontal cortex that dampen orexigenic activity upon consumption of food. Obese subjects showed greater activation of the prefrontal cortex than lean controls, which may be necessary if the orexigenic network needing inhibition is over-active in these individuals. Obese participants also showed an attenuated deactivation of the hypothalamus, thalamus, and cingulate cortex. These findings suggest that orexigenic areas in heavier individuals may not be inhibited to the same extent as in lean individuals after meal ingestion, thus suggesting an impaired satiation response in the obese state.

Collectively, there is accumulating evidence that eating and food choices are controlled by a complex network of neural circuits that are put to the test by the modern environment. We are just beginning to understand why humans may continue to eat energy-dense foods even after they are fully satiated. The decision to continue consuming obesogenic foods in the absence of hunger is likely to be a result of complex integration of neural signals comprising pleasurable feelings of reward, learning, and impaired satiety.

Summary

Maintaining adequate energy supply via regulation of food intake and energy expenditure is crucial for survival and reproduction. The neural control of energy balance is highly complex, occurs across distributed central and peripheral areas, and incorporates multiple domains of control (including homeostatic and hedonic processes). The sheer number of active compounds (such as leptin and GLP-1) involved in the regulation of food intake speaks to the redundancy and complexity of the system. The balance between energy intake and expenditure is under CNS control. Constant bi-directional communication between the brain and the GI tract, as well as the brain and other relevant tissues (i.e., adipose tissue, pancreas, and liver), ensures that the brain constantly perceives and responds accordingly to the energy status/needs of the body. This elegant biological system is subject to disruption by a toxic obesogenic environment, leading to syndromes such as leptin and insulin resistance, and ultimately further exposing obese individuals to further weight gain and T2DM. Recent imaging studies in humans are beginning to examine the influence that higher-order/hedonic brain regions have on homeostatic areas, as well as their responsiveness to homeostatic peripheral signals. With greater understanding of these mechanisms, the field moves closer to understanding and eventually treating the causalities of obesity.

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References

1. Smith GP. The direct and indirect controls of meal size. Neurosci Biobehav Rev. 1996; 20:41–46. [PubMed: 8622828]
2. Grill HJ. Leptin and the systems neuroscience of meal size control. Front Neuroendocrinol. 2010; 31:61–78. [PubMed: 19836413]
3. Moran TH. Gut peptide signaling in the controls of food intake. Obesity. 2006; 14 (Suppl 5):250S–253S. [PubMed: 17021376]
4. Ritter RC. Gastrointestinal mechanisms of satiation for food. Physiol Behav. 2004; 81:249–273. [PubMed: 15159171]
5. Grill HJ, Kaplan JM. The neuroanatomical axis for control of energy balance. Front Neuroendocrinol. 2002; 23:2–40. [PubMed: 11906202]
6. Hajnal A, Smith GP, Norgren R. Oral sucrose stimulation increases accumbens dopamine in the rat. Am J Physiol Regul Integr Comp Physiol. 2004; 286:R31–37. [PubMed: 12933362]
7. Nasse J, Terman D, Venugopal S, Hermann G, Rogers R, Travers JB. Local circuit input to the medullary reticular formation from the rostral nucleus of the solitary tract. Am J Physiol Regul Integr Comp Physiol. 2008; 295:R1391–1408. [PubMed: 18716034]
8. Raybould HE. Gut chemosensing: interactions between gut endocrine cells and visceral afferents. Auton Neurosci. 2010; 153:41–46. [PubMed: 19674941]
9. Grill HJ, Hayes MR. The nucleus tractus solitarius: a portal for visceral afferent signal processing, energy status assessment and integration of their combined effects on food intake. Int J Obes. 2009; 33 (Suppl 1):S11–15.
10. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000; 404:661–671. [PubMed: 10766253]
11. Morton GJ, Schwartz MW. Leptin and the central nervous system control of glucose metabolism. Physiol Rev. 2011; 91:389–411. [PubMed: 21527729]
12. Stefater MA, Seeley RJ. Central nervous system nutrient signaling: the regulation of energy balance and the future of dietary therapies. Annu Rev Nutr. 2010; 30:219–235. [PubMed: 20225935]
13. Elmquist JK, Coppari R, Balthasar N, Ichinose M, Lowell BB. Identifying hypothalamic pathways controlling food intake, body weight, and glucose homeostasis. J Comp Neurol. 2005; 493:63–71. [PubMed: 16254991]
14. Grill HJ. Distributed neural control of energy balance: contributions from hindbrain and hypothalamus. Obesity. 2006; 14 (Suppl 5):216S–221S. [PubMed: 17021370]
15. Myers MG Jr, Munzberg H, Leinninger GM, Leshan RL. The geometry of leptin action in the brain: more complicated than a simple ARC. Cell Metab. 2009; 9:117–123. [PubMed: 19187770]
16. Narayanan NS, Guarnieri DJ, DiLeone RJ. Metabolic hormones, dopamine circuits, and feeding. Front Neuroendocrinol. 2010; 31:104–112. [PubMed: 19836414]
17. Hayes MR, De Jonghe BC, Kanoski SE. Role of the glucagon-like-peptide-1 receptor in the control of energy balance. Physiol Behav. 2010; 100:503–510. [PubMed: 20226203]
18. Hayes MR, Skibicka KP, Leichner TM, et al. Endogenous leptin signaling in the caudal nucleus tractus solitarius and area postrema is required for energy balance regulation. Cell Metab. 2010; 11:77–83. [PubMed: 20074530]
19. Watts AG. Neuropeptides and the integration of motor responses to dehydration. Annu Rev Neurosci. 2001; 24:357–384. [PubMed: 11283315]
20. Bartness TJ, Vaughan CH, Song CK. Sympathetic and sensory innervation of brown adipose tissue. Int J Obes. 2010; 34 (Suppl 1):S36–42.
21. Grill HJ, Skibicka KP, Hayes MR. Imaging obesity: fMRI, food reward, and feeding. Cell Metab. 2007; 6:423–425. [PubMed: 18054310]
22. Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev. 2007; 87:1409–1439. [PubMed: 17928588]
23. Ritter RC, Covasa M, Matson CA. Cholecystokinin: proofs and prospects for involvement in control of food intake and body weight. Neuropeptides. 1999; 33:387–399. [PubMed: 10657516]

24. Raybould HE. Mechanisms of CCK signaling from gut to brain. Curr Opin Pharmacol. 2007; 7:570–574. [PubMed: 17954038]
25. Myers MG, Cowley MA, Munzberg H. Mechanisms of leptin action and leptin resistance. Annu Rev Physiol. 2008; 70:537–556. [PubMed: 17937601]
26. Dieguez C, da Boit K, Novelle MG, Martinez de Morentin PB, Nogueiras R, Lopez M. New insights in ghrelin orexigenic effect. Front Horm Res. 2010; 38:196–205. [PubMed: 20616512]
27. Castaneda TR, Tong J, Datta R, Culler M, Tschop MH. Ghrelin in the regulation of body weight and metabolism. Front Neuroendocrinol. 2010; 31:44–60. [PubMed: 19896496]
28. Gibbs J, Young RC, Smith GP. Cholecystokinin decreases food intake in rats. J Comp Physiol Psychol. 1973; 84:488–495. [PubMed: 4745816]
29. Brenner L, Yox DP, Ritter RC. Suppression of sham feeding by intraintestinal nutrients is not correlated with plasma cholecystokinin elevation. Am J Physiol. 1993; 264:R972–976. [PubMed: 8498606]
30. Liddle RA, Green GM, Conrad CK, Williams JA. Proteins but not amino acids, carbohydrates, or fats stimulate cholecystokinin secretion in the rat. Am J Physiol. 1986; 251:G243–G248. [PubMed: 3740265]
31. Moran TH, Norgren R, Crosby RJ, McHugh PR. Central and peripheral vagal transport of cholecystokinin binding sites occurs in afferent fibers. Brain Res. 1990; 526:95–102. [PubMed: 2078822]
32. Moran TH, Baldessarini AR, Salorio CF, Lowery T, Schwartz GJ. Vagal afferent and efferent contributions to the inhibition of food intake by cholecystokinin. Am J Physiol. 1997; 272:R1245–1251. [PubMed: 9140026]
33. Helm KA, Rada P, Hoebel BG. Cholecystokinin combined with serotonin in the hypothalamus limits accumbens dopamine release while increasing acetylcholine: a possible satiation mechanism. Brain Res. 2003; 963:290–297. [PubMed: 12560135]
34. Esfahani N, Bednar I, Qureshi GA, Sodersten P. Inhibition of serotonin synthesis attenuates inhibition of ingestive behavior by CCK-8. Pharmacol Biochem Behav. 1995; 51:9–12. [PubMed: 7617739]
35. Hayes MR, Moore RL, Shah SM, Covasa M. Serotonin activates 5-HT3, not CCK-A receptors to enhance cholecystokinin-induced satiation. Society For Neuroscience 2004 abstracts. 2004
36. Hayes MR, Savastano DM, Covasa M. Cholecystokinin-induced satiety is mediated through interdependent cooperation of CCK-A and 5-HT3 receptors. Physiol Behav. 2004; 82:663–669. [PubMed: 15327914]
37. Hayes MR, Covasa M. CCK and 5-HT act synergistically to suppress food intake through simultaneous activation of CCK-1 and 5-HT3 receptors. Peptides. 2005; 26:2322–2330. [PubMed: 16269356]
38. Kissileff HR, Carretta JC, Geliebter A, Pi-Sunyer FX. Cholecystokinin and stomach distension combine to reduce food intake in humans. Am J Physiol Regul Integr Comp Physiol. 2003; 285:R992–998. [PubMed: 12920059]
39. Schwartz GJ, Netterville LA, McHugh PR, Moran TH. Gastric loads potentiate inhibition of food intake produced by a cholecystokinin analogue. Am J Physiol. 1991; 261:R1141–1146. [PubMed: 1951762]
40. Emond M, Schwartz GJ, Ladenheim EE, Moran TH. Central leptin modulates behavioral and neural responsivity to CCK. Am J Physiol. 1999; 276:R1545–1549. [PubMed: 10233050]
41. Matson CA, Ritter RC. Long-term CCK-leptin synergy suggests a role for CCK in the regulation of body weight. Am J Physiol Regul Integr Comp Physiol. 1999; 276:R1038–1045.
42. Riedy CA, Chavez M, Figlewicz DP, Woods SC. Central insulin enhances sensitivity to cholecystokinin. Physiol Behav. 1995; 58:755–760. [PubMed: 8559787]
43. Creutzfeldt W. The entero-insular axis in type 2 diabetes--incretins as therapeutic agents. Exp Clin Endocrinol Diabetes. 2001; 109 (Suppl 2):S288–303. [PubMed: 11460578]
44. Mojsov S, Kopczynski MG, Habener JF. Both amidated and nonamidated forms of glucagon-like peptide I are synthesized in the rat intestine and the pancreas. J Biol Chem. 1990; 265:8001–8008. [PubMed: 1692320]

45. Kokrashvili Z, Mosinger B, Margolskee RF. Taste signaling elements expressed in gut enteroendocrine cells regulate nutrient-responsive secretion of gut hormones. Am J Clin Nutr. 2009; 90:822S–825S. [PubMed: 19571229]
46. Larsen PJ, Tang-Christensen M, Holst JJ, Orskov C. Distribution of glucagon-like peptide-1 and other preproglucagon-derived peptides in the rat hypothalamus and brainstem. Neuroscience. 1997; 77:257–270. [PubMed: 9044391]
47. Goke R, Larsen PJ, Mikkelsen JD, Sheikh SP. Distribution of GLP-1 binding sites in the rat brain: evidence that exendin-4 is a ligand of brain GLP-1 binding sites. Eur J Neurosci. 1995; 7:2294–2300. [PubMed: 8563978]
48. Merchenthaler I, Lane M, Shughrue P. Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. J Comp Neurol. 1999; 403:261–280. [PubMed: 9886047]
49. Hayes MR, Skibicka KP, Grill HJ. Caudal brainstem processing is sufficient for behavioral, sympathetic and parasympathetic responses driven by peripheral and hindbrain glucagon-like-peptide-1 receptor stimulation. Endocrinology. 2008; 149:4059–68. [PubMed: 18420740]
50. Kinzig KP, D'Alessio DA, Seeley RJ. The diverse roles of specific GLP-1 receptors in the control of food intake and the response to visceral illness. J Neurosci. 2002; 22:10470–10476. [PubMed: 12451146]
51. Schick RR, Zimmermann JP, vorm Walde T, Schusdziarra V. Peptides that regulate food intake: glucagon-like peptide 1-(7-36) amide acts at lateral and medial hypothalamic sites to suppress feeding in rats. Am J Physiol Regul Integr Comp Physiol. 2003; 284:R1427–1435. [PubMed: 12776726]
52. Abbott CR, Monteiro M, Small CJ, et al. The inhibitory effects of peripheral administration of peptide YY(3-36) and glucagon-like peptide-1 on food intake are attenuated by ablation of the vagal-brainstem-hypothalamic pathway. Brain Res. 2005; 1044:127–131. [PubMed: 15862798]
53. 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:R1695–1706. [PubMed: 15718384]
54. Imeryuz N, Yegen BC, Bozkurt A, Coskun T, Villanueva-Penacarrillo ML, Ulusoy NB. Glucagon-like peptide-1 inhibits gastric emptying via vagal afferent-mediated central mechanisms. Am J Physiol. 1997; 273:G920–927. [PubMed: 9357836]
55. Sandoval DA, Bagnol D, Woods SC, D'Alessio DA, Seeley RJ. Arcuate GLP-1 receptors regulate glucose homeostasis but not food intake. Diabetes. 2008; 57:2046–54. [PubMed: 18487451]
56. Knauf C, Cani PD, Perrin C, et al. Brain glucagon-like peptide-1 increases insulin secretion and muscle insulin resistance to favor hepatic glycogen storage. J Clin Invest. 2005; 115:3554–3563. [PubMed: 16322793]
57. Komatsu R, Matsuyama T, Namba M, et al. Glucagonostatic and insulinotropic action of glucagonlike peptide I-(7-36)-amide. Diabetes. 1989; 38:902–905. [PubMed: 2661287]
58. Nakabayashi H, Nishizawa M, Nakagawa A, Takeda R, Niijima A. Vagal hepatopancreatic reflex effect evoked by intraportal appearance of tGLP-1. Am J Physiol. 1996; 271:E808–813. [PubMed: 8944665]
59. Balkan B, Li X. Portal GLP-1 administration in rats augments the insulin response to glucose via neuronal mechanisms. Am J Physiol Regul Integr Comp Physiol. 2000; 279:R1449–1454. [PubMed: 11004015]
60. Blonde L, Klein EJ, Han J, et al. Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. Diabetes Obes Metab. 2006; 8:436–447. [PubMed: 16776751]
61. Montanya E, Sesti G. A review of efficacy and safety data regarding the use of liraglutide, a once-daily human glucagon-like peptide 1 analogue, in the treatment of type 2 diabetes mellitus. Clin Ther. 2009; 31:2472–2488. [PubMed: 20109994]
62. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009; 374:39–47. [PubMed: 19515413]

63. Hayes MR, Kanoski SE, Alhadeff AL, Grill HJ. Comparative effects of the long-acting GLP-1 receptor ligands, liraglutide and exendin-4, on food intake and body weight suppression in rats. Obesity. 2011:19.
64. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994; 372:425–432. [PubMed: 7984236]
65. Banks WA. Blood-brain barrier as a regulatory interface. Forum Nutr. 2010; 63:102–110. [PubMed: 19955778]
66. Date Y, Kojima M, Hosoda H, et al. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology. 2000; 141:4255–4261. [PubMed: 11089560]
67. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999; 402:656–660. [PubMed: 10604470]
68. Guan XM, Yu H, Palyha OC, et al. Distribution of mRNA encoding the growth hormone secretagogue receptor in brain and peripheral tissues. Brain Res Mol Brain Res. 1997; 48:23–29. [PubMed: 9379845]
69. Lin Y, Matsumura K, Fukuhara M, Kagiyama S, Fujii K, Iida M. Ghrelin acts at the nucleus of the solitary tract to decrease arterial pressure in rats. Hypertension. 2004; 43:977–982. [PubMed: 14993197]
70. Jerlhag E, Egecioglu E, Dickson SL, Douhan A, Svensson L, Engel JA. 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]
71. Tschop M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. Nature. 2000; 407:908–913. [PubMed: 11057670]
72. Wren AM, Seal LJ, Cohen MA, et al. Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab. 2001; 86:5992. [PubMed: 11739476]
73. Faulconbridge LF, Cummings DE, Kaplan JM, Grill HJ. Hyperphagic effects of brainstem ghrelin administration. Diabetes. 2003; 52:2260–2265. [PubMed: 12941764]
74. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes. 2001; 50:1714–1719. [PubMed: 11473029]
75. Neel JV. Diabetes mellitus: a “thrifty” genotype rendered detrimental by “progress”? Am J Hum Genet. 1962; 14:353–362. [PubMed: 13937884]
76. Brownell, KD. Get slim with higher taxes. New York Times; Dec 15th. 1994 p. A 29
77. Egger G, Swinburn B. An “ecological” approach to the obesity pandemic. BMJ. 1997; 315:477–480. [PubMed: 9284671]
78. Kringelbach ML. Food for thought: hedonic experience beyond homeostasis in the human brain. Neuroscience. 2004; 126:807–819. [PubMed: 15207316]
79. Saper CB, Chou TC, Elmquist JK. The need to feed: homeostatic and hedonic control of eating. Neuron. 2002; 36:199–211. [PubMed: 12383777]
80. Berthoud HR. Mind versus metabolism in the control of food intake and energy balance. Physiol Behav. 2004; 81:781–793. [PubMed: 15234184]
81. Lenard NR, Berthoud HR. Central and peripheral regulation of food intake and physical activity: pathways and genes. Obesity. 2008; 16 (Suppl 3):S11–22. [PubMed: 19190620]
82. Woods SC, D’Alessio DA. Central control of body weight and appetite. J Clin Endocrinol Metab. 2008; 93:S37–50. [PubMed: 18987269]
83. Killgore WD, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. Cortical and limbic activation during viewing of high- versus low-calorie foods. Neuroimage. 2003; 19:1381–1394. [PubMed: 12948696]
84. O’Doherty JP, Deichmann R, Critchley HD, Dolan RJ. Neural responses during anticipation of a primary taste reward. Neuron. 2002; 33:815–826. [PubMed: 11879657]
85. Rolls, ET. The Brain and Emotion. New York: Oxford University Press; 1990.
86. Rolls ET. The orbitofrontal cortex and reward. Cereb Cortex. 2000; 10:284–294. [PubMed: 10731223]

87. Small DM, Jones-Gotman M, Dagher A. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. Neuroimage. 2003; 19:1709–1715. [PubMed: 12948725]
88. Batterham RL, ffytche DH, Rosenthal JM, et al. PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. Nature. 2007; 450:106–109. [PubMed: 17934448]
89. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev. 1998; 28:309–369. [PubMed: 9858756]
90. Nestler EJ. Molecular basis of long-term plasticity underlying addiction. Nat Rev Neurosci. 2001; 2:119–128. [PubMed: 11252991]
91. Grigson PS, Twining RC. Cocaine-induced suppression of saccharin intake: a model of drug-induced devaluation of natural rewards. Behav Neurosci. 2002; 116:321–333. [PubMed: 11996317]
92. Del-Fava F, Hasue RH, Ferreira JG, Shammah-Lagnado SJ. Efferent connections of the rostral linear nucleus of the ventral tegmental area in the rat. Neuroscience. 2007; 145:1059–1076. [PubMed: 17270353]
93. Kelley AE. Memory and addiction: shared neural circuitry and molecular mechanisms. Neuron. 2004; 44:161–179. [PubMed: 15450168]
94. Usuda I, Tanaka K, Chiba T. Efferent projections of the nucleus accumbens in the rat with special reference to subdivision of the nucleus: biotinylated dextran amine study. Brain Res. 1998; 797:73–93. [PubMed: 9630528]
95. Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. J Nutr. 2009; 139:629–632. [PubMed: 19176746]
96. Holsen LM, Zarcone JR, Thompson TI, et al. Neural mechanisms underlying food motivation in children and adolescents. Neuroimage. 2005; 27:669–676. [PubMed: 15993629]
97. LaBar KS, Gitelman DR, Parrish TB, Kim YH, Nobre AC, Mesulam MM. Hunger selectively modulates corticolimbic activation to food stimuli in humans. Behav Neurosci. 2001; 115:493–500. [PubMed: 11345973]
98. Porubska K, Veit R, Preissl H, Fritsche A, Birbaumer N. Subjective feeling of appetite modulates brain activity: an fMRI study. Neuroimage. 2006; 32:1273–1280. [PubMed: 16815041]
99. Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M. Changes in brain activity related to eating chocolate: from pleasure to aversion. Brain. 2001; 124:1720–1733. [PubMed: 11522575]
100. Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. J Clin Invest. 2008; 118:2583–2591. [PubMed: 18568078]
101. Stoeckel LE, Weller RE, Cook EW 3rd, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage. 2008; 41:636–647. [PubMed: 18413289]
102. Matsuda M, Liu Y, Mahankali S, et al. Altered hypothalamic function in response to glucose ingestion in obese humans. Diabetes. 1999; 48:1801–1806. [PubMed: 10480611]
103. Liu Y, Gao JH, Liu HL, Fox PT. The temporal response of the brain after eating revealed by functional MRI. Nature. 2000; 405:1058–1062. [PubMed: 10890447]
104. Smeets PA, de Graaf C, Stafleu A, van Osch MJ, van der Grond J. Functional MRI of human hypothalamic responses following glucose ingestion. Neuroimage. 2005; 24:363–368. [PubMed: 15627579]
105. Gautier JF, Chen K, Salbe AD, et al. Differential brain responses to satiation in obese and lean men. Diabetes. 2000; 49:838–846. [PubMed: 10905495]
106. Gautier JF, Del Parigi A, Chen K, et al. Effect of satiation on brain activity in obese and lean women. Obes Res. 2001; 9:676–684. [PubMed: 11707534]
107. Tataranni PA, Gautier JF, Chen K, et al. Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. Proc Natl Acad Sci U S A. 1999; 96:4569–4574. [PubMed: 10200303]

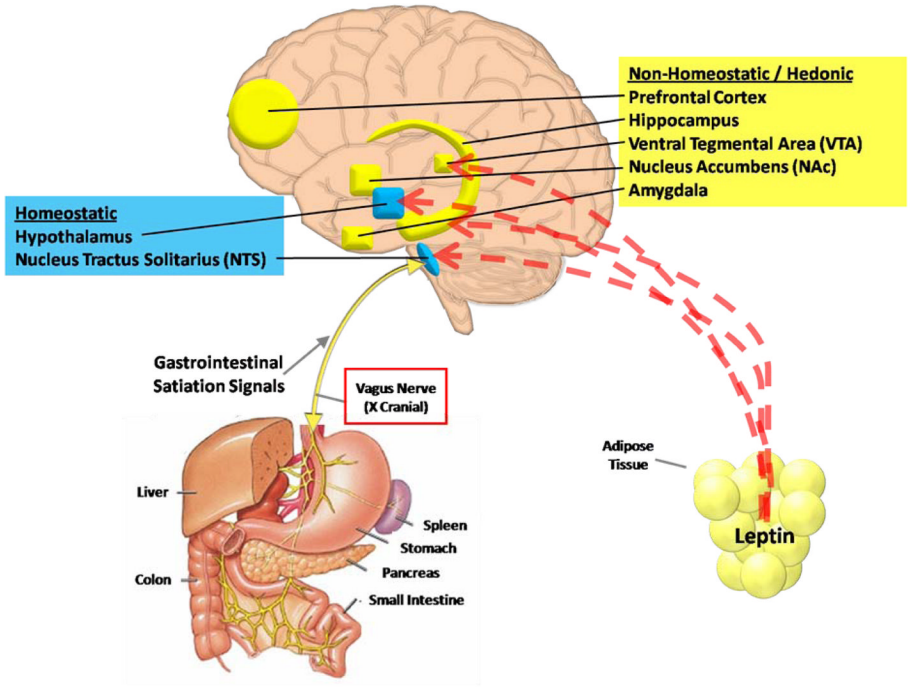

Figure 1.

The distributed CNS nuclei control energy intake. The circulating energy-status signals, as well as vagally-mediated satiation signals, can act either directly or indirectly on both homeostatic nuclei (hypothalamus and nucleus tractus solitarius [NTS] in the brainstem) and hedonic/non-homeostatic nuclei.