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Central nervous system control of food intake

[Insight Review Article]

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Abstract

New information regarding neuronal circuits that control food intake and their hormonal regulation has extended our understanding of energy homeostasis, the process whereby energy intake is matched to energy expenditure over time. The profound obesity that results

in rodents (and in the rare human case as well) from mutation of key signalling molecules involved in this regulatory system highlights its importance to human health. Although each new signalling pathway discovered in the hypothalamus is a potential target for drug development in the treatment of obesity, the growing number of such signalling molecules indicates that food intake is controlled by a highly complex process. To better understand how energy homeostasis can be achieved, we describe a model that delineates the roles of individual hormonal and neuropeptide signalling pathways in the control of food intake and the means by which obesity can arise from inherited or acquired defects in their function.

For most of us, the composition and amount of food that we eat varies considerably from one meal to the next and from one day to the next. Our common experience, therefore, seems at odds with the hypothesis that food intake is highly regulated. Emotions, social factors, time of day, convenience and cost are but a few of the variables that are not biologically regulated, but nonetheless affect meal-to-meal energy intake. As a consequence, daily energy intake is variable both within and among individuals, and is not well correlated with daily energy expenditure [1](#). Despite short-term mismatches in energy balance, however, most of us match cumulative energy intake to energy expenditure with great precision when measured over a period that spans many meals [1](#). This phenomenon reflects an active regulatory process, termed energy homeostasis, that promotes stability in the amount of body energy stored in the form of fat.

Although it is overly simplistic to reduce a behaviour as complex as feeding to a series of molecular interactions, discoveries over the past few years have identified signalling molecules that affect food intake and that are critical for normal energy homeostasis. The application of molecular genetics to mice has been especially important in this effort. For example, several monogenic forms of human obesity were identified by searching for mutations homologous to those causing obesity in mice [2-5](#). Although such monogenic obesity syndromes are rare (see review by Barsh *et al.*, pp. 644-651), the successful use of murine models to study human obesity indicates that substantial homology exists across mammalian species in the functional organization of the weight-regulatory system. More importantly, the identification of molecules that control food intake has generated new targets for drug development in the treatment of obesity and related disorders. Optimism that we may soon enter an era of improved obesity treatment, therefore, seems justified.

Because of the enormous toll on human health taken by obesity and related disorders, an improved understanding of the control of food intake is an important priority. However, the growing number of molecules implicated in energy homeostasis raises nearly limitless possibilities for how body-weight regulation might occur. The aim of this article is to review these advances and to present them in the context of a model for long-term maintenance of energy homeostasis.

Model for energy homeostasis [1](#)

The increase of food intake (hyperphagia) triggered by a period of fasting is a simple but compelling example of food-intake regulation. The consequent recovery of lost body weight to baseline values, accompanied by the gradual return to normal levels of energy intake [6](#), is testimony to a regulatory process that is both precise and robust. To explain this phenomenon, Kennedy proposed [7](#) in 1953 that inhibitory signals generated in proportion to body fat stores act in the brain to reduce food intake. Thus, when weight loss induced by caloric restriction reduces the level of these inhibitory signals, food intake increases until the energy deficit is corrected. This model, however, does not explain how energy intake is controlled during individual meals. Twenty years later, Gibbs and Smith proposed [8](#) that

signals generated during a meal (termed 'satiety factors'), including peptides secreted from the gastrointestinal tract, provide information to the brain that inhibits feeding and leads to meal termination. A model that seems to unite these two hypotheses is illustrated schematically in [Fig. 1](#).

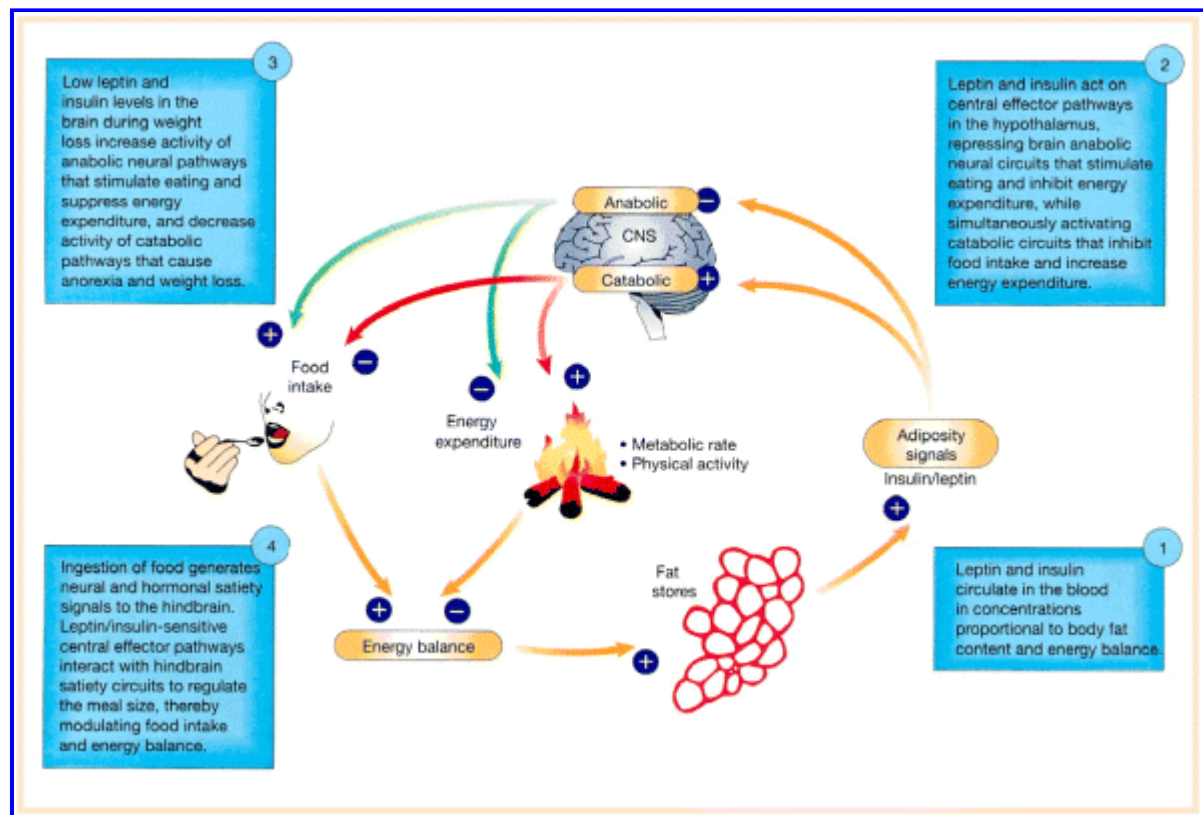


Figure 1 Model showing how a change in body adiposity is coupled to compensatory changes of food intake. Leptin and insulin are adiposity signals, secreted in proportion to body fat content, which act in the hypothalamus to stimulate catabolic, while inhibiting anabolic, effector pathways. These pathways have opposing effects on energy balance (the difference between calories consumed and energy expended) that in turn determines the amount of body fuel stored as fat.

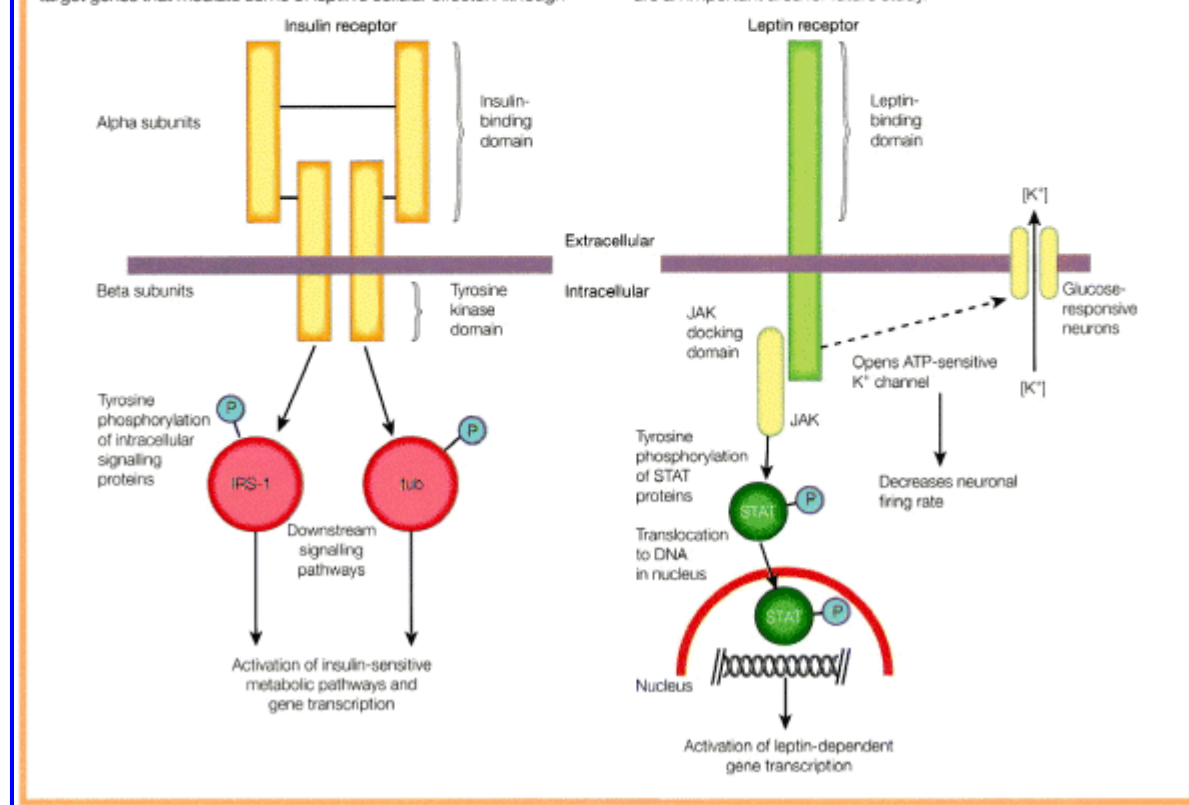
Adiposity signals: leptin and insulin [↑](#)

The pancreatic hormone, insulin, which enters the brain from the circulation [9](#) and acts there to reduce energy intake [10](#), was the first hormonal signal to be implicated in the control of body weight by the central nervous system (CNS). The subsequent demonstration that the profound hyperphagia and obesity of *ob/ob* mice results from autosomal recessive mutation of the gene encoding leptin [11](#), a hormone secreted by adipocytes, provided compelling evidence of a second adiposity signal. Subsequent studies demonstrated that both insulin and leptin fulfil criteria that should be met by any candidate adiposity signal. Both hormones circulate at levels proportional to body fat content [12,13](#) and enter the CNS in proportion to their plasma level [9,14](#). Leptin receptors and insulin receptors (see [Box 1](#)) are expressed by brain neurons involved in energy intake [15-17](#), and administration of either peptide directly into the brain reduces food intake [10,18,19](#), whereas deficiency of either hormone does the opposite [11,20](#). To date, insulin and leptin are the only molecules that fulfil these criteria.

The insulin receptor comprises an extracellular α -subunit involved in ligand binding and an intracellular β -subunit that transduces the insulin signal to the cell (Box 1 Figure). The β -subunit has intrinsic tyrosine kinase activity that, upon insulin binding, activates intracellular signalling proteins by phosphorylating them on tyrosine residues¹¹⁵. These proteins include insulin-receptor substrate (IRS)-1, which is present in neurons and in peripheral tissues¹¹⁶. The neuronal protein encoded by the *Tub* gene is also tyrosine-phosphorylated in response to activation of the insulin receptor¹¹⁷. Because a loss-of-function mutation of *Tub* causes obesity in *tubby* mice, there is new support for the hypothesis that defective insulin signalling in the brain causes obesity.

Unlike insulin receptors, leptin receptors are members of the cytokine-receptor superfamily and do not have intrinsic tyrosine kinase activity¹¹⁸. However, the leptin receptor does have docking sites for janus kinases (JAK), a family of tyrosine kinases involved in intracellular cytokine signalling¹¹⁹. Activated JAK phosphorylates members of the signal transduction and transcription (STAT) family of intracellular proteins. STAT proteins, in turn, stimulate transcription of target genes that mediate some of leptin's cellular effects. Although

regulation of hypothalamic neuropeptide gene expression by leptin is well described, the role of JAK-STAT signalling in this response remains uncertain, as leptin can affect neuronal firing rate independently of its transcriptional effects. For example, a subset of 'glucose-responsive' neurons in the hypothalamus become hyperpolarized (and therefore decrease their firing rate) within minutes of leptin application¹²⁰. Glucose influences the membrane potential of glucose-responsive neurons indirectly through its oxidation to generate ATP, which in turn controls the activity of ATP-sensitive potassium channels (K_{ATP}) in the plasma membrane¹²¹. Closure of K_{ATP} channels in response to increasing intracellular concentrations of ATP (relative to ADP) raises intracellular $[K^+]$, which depolarizes the cell and increases its firing rate. Because leptin maintains K_{ATP} channels in the open configuration¹²⁰, positively charged K^+ ions diffuse out of the cell and lower its membrane potential. This effect on K_{ATP} channels can be detected even in isolated patches of plasma membrane, excluding a mechanism involving transcriptional effects of leptin. The relationships among leptin signalling through the JAK-STAT pathway, its effects on neuronal firing rate, and its control of neuropeptide gene expression are an important area for future study.



Box 1 Leptin- and insulin-receptor signalling

Different mechanisms underlie the association of insulin and leptin with body fat content [21](#). The effect of weight gain to reduce insulin sensitivity seems to explain how insulin, but not leptin, varies according to body fat stores [22](#). As weight increases, insulin secretion must increase in both the basal state and in response to meals to compensate for insulin resistance if normal glucose homeostasis is to be maintained [23,24](#). Failure of the pancreatic [β]-cell to achieve this adaptive increase of insulin secretion causes hyperglycaemia, and probably contributes to the association of type 2 diabetes with obesity. Increased insulin secretion as obesity progresses is thus hypothesized to increase insulin delivery to the brain, where it helps to limit further weight gain.

Mechanisms involved in leptin secretion are quite different. The rate of insulin-stimulated glucose utilization in adipocytes is a key factor linking leptin secretion to body fat mass [25](#). Although the mechanism is incompletely understood, it may involve glucose flux through the hexosamine pathway [26](#). Because acute changes of energy balance markedly affect adipocyte

glucose metabolism, leptin secretion can become transiently dissociated from levels of total body fat. For example, food deprivation lowers plasma leptin concentrations in both rodents and humans much more rapidly and to a greater extent than would be expected from the decrease of body fat content. This exaggerated early decline of leptin levels would enable compensatory responses to be activated before energy stores are substantially depleted.

Several observations indicate that leptin has a more important role than insulin in the CNS control of energy homeostasis. For example, leptin deficiency causes severe obesity, with hyperphagia that persists despite high insulin levels. In contrast, obesity is not induced by insulin deficiency. But such comparisons are complicated by the critical role that insulin has in promoting both fat storage and leptin synthesis by fat cells. Because fat deposition requires insulin, weight gain cannot occur when insulin deficiency is present, even if food is consumed in large amounts. For example, in uncontrolled diabetes mellitus (the disease induced by the loss of insulin), food intake increases markedly [27](#), but levels of both body adiposity and plasma leptin remain low in rats [28](#) and humans [29](#). Rather than being stored as fat, excess calories ingested in this context contribute to elevated blood glucose levels, and ultimately, much of this glucose is lost in the urine. Because both insulin and leptin levels are low in this type of diabetes, the long-recognized syndrome of 'diabetic hyperphagia'[27](#) could potentially result from reduced CNS signalling by insulin, leptin, or by both hormones. A recent study sought to clarify this issue by selectively replenishing leptin (but not insulin) to nondiabetic levels through exogenous leptin infusion in a rat model of uncontrolled, insulin-deficient diabetes [30](#). Because this intervention prevented the development of diabetic hyperphagia, it was concluded that deficiency of leptin, but not insulin, is required for hyperphagia in this model. Thus, although both leptin and insulin probably participate in the CNS control of energy homeostasis, available data indicate that leptin has the more critical role.

Leptin resistance and obesity [↑](#)

The hypothesis that leptin resistance can occur in association with obesity was first suggested by the finding of elevated plasma leptin levels in obese humans [13](#). This hypothesis suggests that some cases of human obesity may be due to reduced leptin action in the brain, and that affected individuals are unlikely to respond to pharmacological treatment with leptin. Resistance to leptin is clearly documented in mice (for example, *db/db*)[19](#) and rats (for example, *fa/fa*)[31](#) bearing mutant leptin receptors, but also in mice that develop obesity for other reasons. These include mice with genetic ablation of thermogenic brown adipose tissue [32](#), mice that lack melanocortin-4 (MC4) receptors [33](#), agouti (*A^y/a*) mice [34](#) (see later) and mice fed a highly palatable high-fat diet [19](#).

Several mechanisms may contribute to leptin resistance. By decreasing the ability of circulating leptin to enter brain interstitial fluid, where it can bind to neuronal leptin receptors, impaired leptin transport across endothelial cells of the blood-brain barrier is one potential mechanism. Several studies indicate that, like insulin [9](#), leptin uptake into the brain is facilitated by leptin receptors expressed by endothelial cells [35](#) in the blood-brain barrier that function as leptin transporters. Whether dysfunction of this transport process can lead to obesity remains to be determined, but the finding that obese humans have leptin levels in cerebrospinal fluid that are low in comparison to plasma [36](#) is consistent with this possibility.

Reduced leptin-receptor signal transduction is another potential cause of leptin resistance. This has been documented not only in the brain of rodents bearing mutant leptin receptors, but also as an acquired response to leptin-receptor activation. Like some other cytokine receptors, activation of the leptin receptor induces expression of a protein that inhibits further leptin signal transduction, termed 'suppressor of cytokine signalling-3' (SOCS-3)[37](#). The potential contribution of SOCS-3 to acquired forms of leptin resistance and obesity is an

active area of study.

Upon activation of leptin receptors in the brain, a series of integrated neuronal responses is probably required for food intake and energy balance to be affected. Failure of one or more neuronal systems in this circuit to respond to the leptin signal will therefore manifest as leptin resistance. The key role that these neuronal effector pathways have in energy homeostasis makes them an important priority for study and is the focus of the following discussion.

Neuropeptide effectors of adiposity signals

Several distinct hypothalamic neuropeptide-containing pathways have emerged as candidate mediators of leptin and insulin action in the CNS ([Table 1](#)).

Molecule	Regulation by adiposity signals
Orexigenic	
NPY*	↓
AGRP*	↓
MCH	↓
Hypocretin 1 and 2/orexin A and B	↓
Galanin	?
Noradrenaline	?
Anorexigenic	
α-MSH*	↑
CRH*	↑
TRH*	↑
CART*	↑
IL-1β*	↑
Urocortin*	?
Glucagon-like peptide 1	?
Oxytocin	?
Neurotensin	?
Serotonin	?
Orexigenic refers to molecules that promote increased energy intake; anorexigenic implies the opposite. An asterisk designates documented, coordinated effects on both food intake and energy expenditure that promote a change in energy stores; arrows designate direction of effect exerted by one or both of the adiposity signals, leptin and insulin.	

Table 1 Neuropeptides implicated in the control of energy homeostasis

Neuropeptide Y stimulates food intake

Prominent among anabolic effector pathways is a circuit containing neuropeptide Y (NPY). Injection of NPY into cerebral ventricles or directly into the hypothalamus of rats potently stimulates food intake [38](#) and decreases energy expenditure while simultaneously inducing lipogenic enzymes in liver and white adipose tissue [39](#). Consequently, continuous or repeated central administration of NPY leads readily to obesity [38,40](#). Because NPY gene expression and secretion of the NPY peptide in the hypothalamus are increased during active depletion of body fat stores [41,42](#) and/or reduced leptin/insulin signalling to the brain [43](#), NPY meets the criteria for an anabolic signalling molecule. Moreover, leptin inhibits arcuate nucleus NPY gene expression [44,45](#) and genetic knockout of NPY reduces hyperphagia and

obesity in *ob/ob* mice [46](#), indicating that the full response to leptin deficiency requires NPY signalling ([Fig. 2a](#)). The hyperphagic response to insulin-deficient diabetes is similarly accompanied by increased hypothalamic NPY synthesis and release [47](#), and this response is blocked by insulin administration, either systemically or directly into the brain [20](#). The finding that mice that lack NPY (but are otherwise genetically normal) have intact feeding responses, however, raises questions about the need for NPY when leptin or insulin levels are normal [48](#). Alternatively, congenital absence of a major neuropeptide such as NPY may elicit compensatory responses that mask the consequences of its deficiency, and further study is required to resolve this issue. Agouti-related protein (AGRP), orexin (also known as 'hypocretin') and melanin-concentrating hormone (MCH) have subsequently been added to the list of candidate anabolic effector signalling molecules ([Table 1](#)).

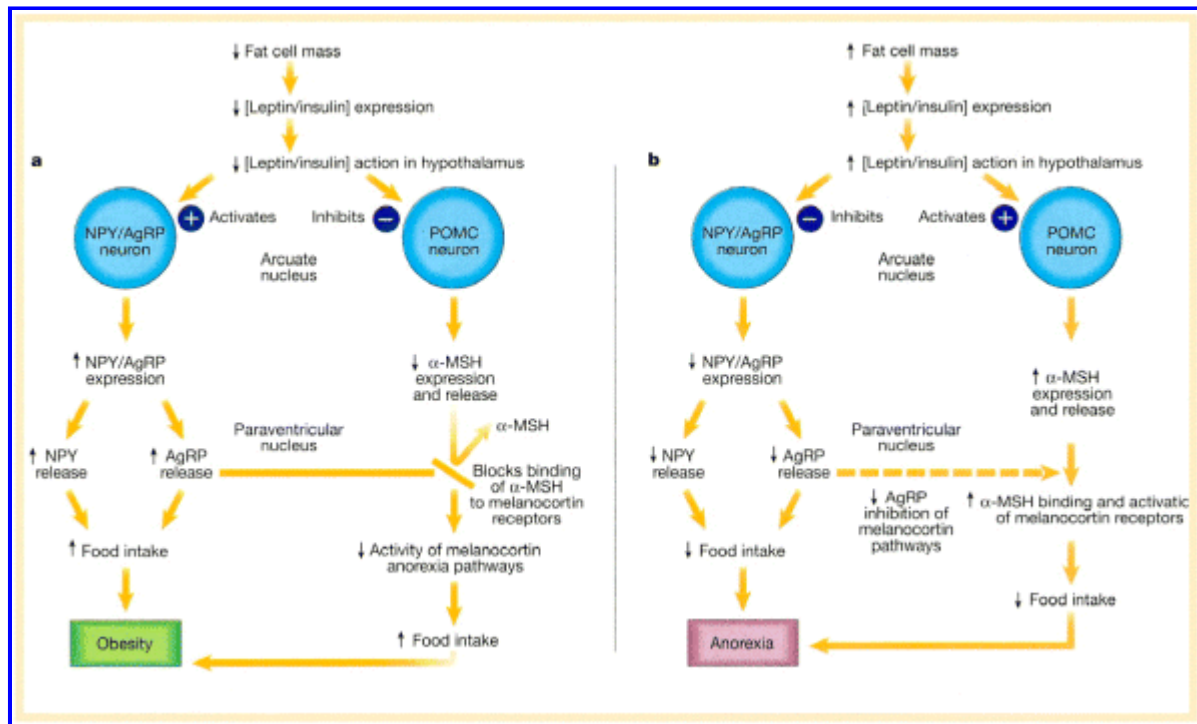


Figure 2 Role of arcuate nucleus neurons in adiposity signalling. **a**, Activity of leptin/insulin-sensitive adiposity signalling pathways in hypothalamus under conditions of leptin/insulin deficiency. **b**, Increased action of leptin/insulin in arcuate nucleus inhibits the NPY/AGRP anabolic pathway and stimulates the POMC catabolic pathway, resulting in reduced food intake and anorexia.

Melanocortins suppress food intake [49](#)

Candidate catabolic effector signalling molecules have an opposite set of characteristics. Melanocortins such as [alpha]-melanocyte-stimulating hormone ([alpha]-MSH)[49](#), as well as corticotropin-releasing hormone (CRH)[50](#), thyrotropin-releasing hormone (TRH)[51](#), cocaine- and amphetamine-regulated transcript (CART)[52](#) and interleukin-1[beta][53](#) are among a growing list of peptides that promote negative energy balance. Neuronal synthesis of these peptides increases in response to increased adiposity signalling in the brain. Among these, the melanocortin system stands out as being remarkable both for its complexity and its importance to energy homeostasis.

Melanocortins are peptides (such as [alpha]-MSH) that are cleaved from the pro-opiomelanocortin (POMC) precursor molecule and that exert their effects by binding to members of a family of melanocortin receptors [49](#). A role for melanocortin signalling in the control of energy homeostasis first emerged after the cloning of the MC3- and MC4-receptor genes and the demonstration that they are expressed primarily in the brain [54](#). This discovery was followed by evidence that a synthetic agonist of these receptors suppresses food intake,

whereas a synthetic antagonist has the opposite effect [55](#). The report that mice lacking the MC4 receptor (owing to gene targeting) are hyperphagic and very obese [56](#) indicates that tonic signalling by MC4 receptors limits food intake and body fat mass. Mice heterozygous for the deleted MC4 allele also become obese, although less so than homozygous knockouts [56](#). Lack of a full complement of central MC4 receptors, therefore, predisposes to hyperphagia and pathological weight gain. This finding has since been extended to humans with MC4-receptor mutations [4,5](#).

Further evidence for the importance of melanocortin signalling came from studies of agouti (*A^y/a*) mice, an autosomal dominant model of genetic obesity characterized by a yellow coat colour and an obese phenotype. Cloning of the *agouti* gene [57](#) identified a protein ('agouti') that functions as an antagonist of cutaneous MC1 receptors and normally is expressed by hair follicles. By reducing MC1 signalling, increased cutaneous agouti lightens the coat colour. Agouti mice, however, express agouti in tissues throughout the body and consequently develop both a yellow coat colour and obesity (owing to ectopic agouti production within the brain, where it antagonizes MC4 receptors)[49](#) ([Fig. 2b](#)).

The subsequent cloning of the *Agrp* gene [58](#) identified a peptide, AGRP, with homology to *agouti* that is an antagonist of MC3 and MC4 receptors [59](#). The demonstration that hypothalamic AGRP expression, like that of NPY and POMC, is localized to the arcuate nucleus [58](#), and that it is upregulated by fasting [60,61](#) and by leptin deficiency [58](#), indicates that antagonism of CNS melanocortin receptors is important in body-weight regulation. Consistent with its role as an anabolic signalling molecule, AGRP causes hyperphagia when administered intracerebroventricularly (i.c.v.)[62,63](#) or expressed transgenically [59](#), and the increase of food intake following a single i.c.v. injection of AGRP is sustained for up to a week [62](#). Although NPY is described as the most potent orexigenic molecule (that is, a molecule that stimulates increased energy intake) when the feeding response is measured over a few hours, its effects are short-lived in comparison to those of AGRP. AGRP must therefore be considered the most robust orexigenic molecule if potency is measured as the cumulative increment of energy intake after a single i.c.v. injection. The mechanism underlying the extraordinary duration of action of AGRP remains a fascinating area for further investigation.

Neuropeptide signalling pathways in the hypothalamus [↑](#)

Brain lesioning and stimulation studies performed some six decades ago first implicated the hypothalamus as a major centre controlling food intake and body weight ([Fig. 3](#)). As summarized in a classic paper by Stellar [64](#), these studies identified the ventromedial hypothalamic nucleus (VMN) as the 'satiety centre', while the lateral hypothalamic area (LHA) was termed the 'hunger centre' (reviewed in ref. [50](#)). These designations reflected the ability of electrical stimulation of the VMN to suppress food intake, and of bilateral VMN lesions to induce hyperphagia and obesity. Conversely, stimulation or lesioning of the LHA induced the opposite set of responses. As our knowledge of specific neuronal subpopulations involved in energy homeostasis has expanded, the notion of specific 'centres' of the brain that control food intake and body weight has been replaced by that of discrete neuronal pathways that generate integrated responses to afferent input related to changing body fuel stores [65](#).

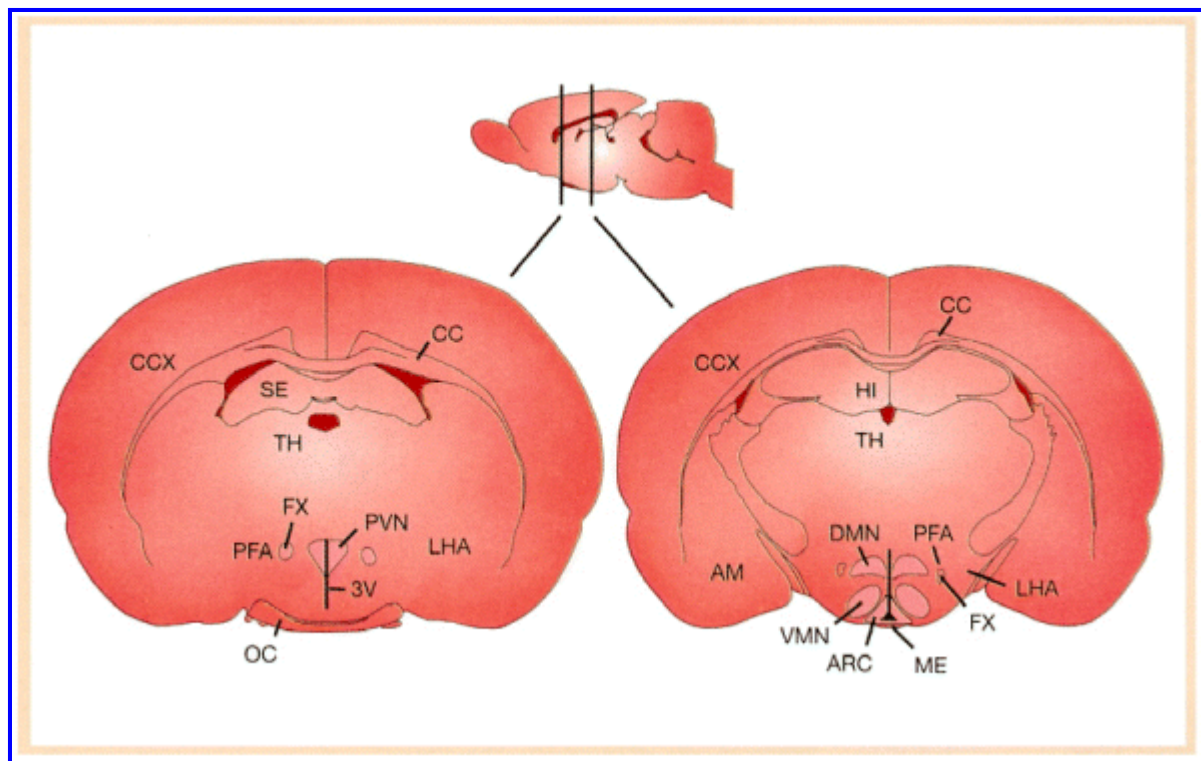


Figure 3 Diagrams of rat brain, showing major hypothalamic regions implicated in adiposity signalling and regulation of food intake. The small figure at the top is a longitudinal view of a rat brain, with olfactory bulb at the anterior end on the left and the caudal hindbrain on the right. Cross-sections of the brain at two levels (indicated by vertical lines) are shown at the left and right. First-order neurons responding to adiposity signals are located in the arcuate nucleus (ARC) and project anteriorly to the PVN as well as the PFA adjacent to the fornix (FX) and the LHA. Other regions implicated in regulating food intake include the ventromedial nucleus (VMN) and dorsomedial nucleus (DMN). Abbreviations of brain structures: AM, amygdala; CC, corpus callosum; CCX, cerebral cortex; HI, hippocampus; ME, median eminence; OC, optic chiasm; SE, septum; TH, thalamus; 3V, third ventricle.

Transduction of adiposity signals into a neuronal response [↑](#)

Situated adjacent to the floor of the third ventricle, the arcuate nucleus is an elongate ('arc-like') collection of neuronal cell bodies occupying approximately one-half of the length of the hypothalamus. NPY and AGRP are co-localized in arcuate nucleus neurons [60,61](#), demonstrating that a single neuronal cell type can contain multiple anabolic effector molecules. The subsequent finding that POMC and CART are co-localized in a distinct, but adjacent, subset of arcuate nucleus neurons [66](#) indicates that circuits originating in this brain area have highly specialized roles in energy homeostasis ([Fig. 4](#)).

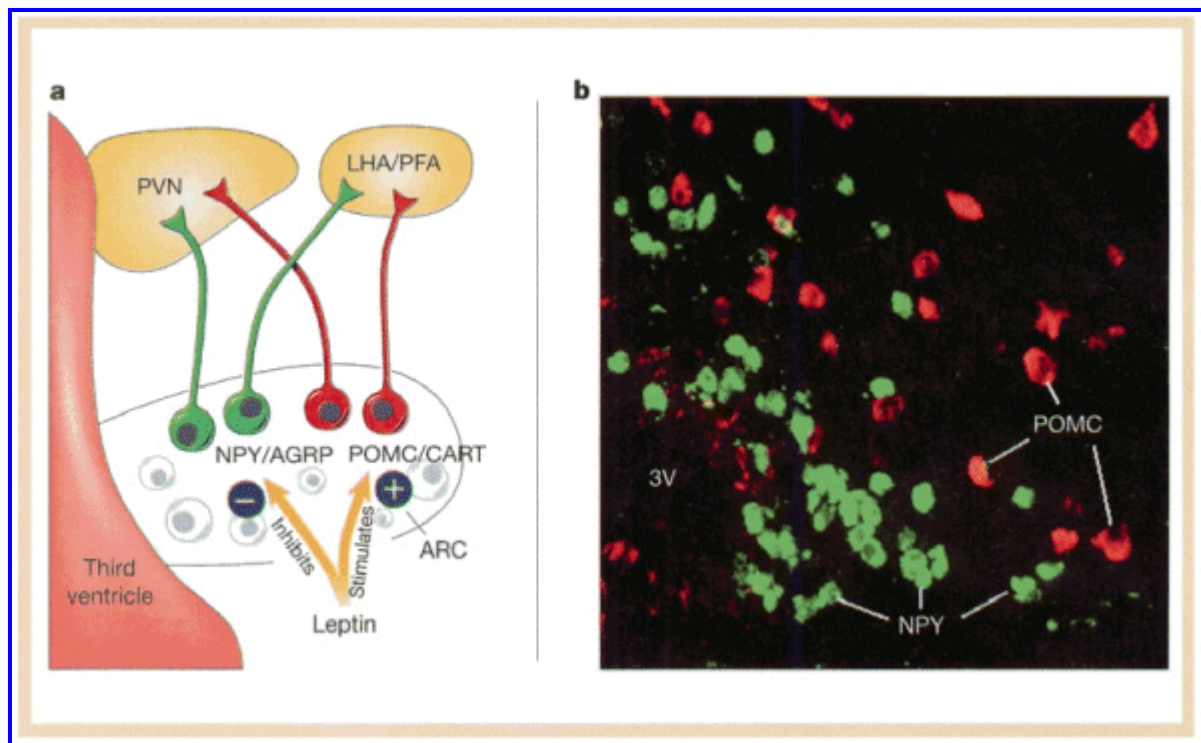


Figure 4 NPY/AGRP and POMC/CART neurons in the arcuate nucleus, adjacent to the third ventricle, are first-order neurons in the hypothalamic response to the circulating adiposity signals insulin and leptin. **a**, Populations of first-order NPY/AGRP (green) and POMC/CART (red) neurons in the arcuate nucleus (ARC) are regulated by leptin and project to the PVN and to the LHA and PFA, which are locations of second-order hypothalamic neuropeptide neurons involved in the regulation of food intake and energy homeostasis. **b**, Fluorescence *in situ* hybridization detection of mRNAs encoding NPY (green cells) and POMC (red cells) in the arcuate nucleus, adjacent to the third ventricle (3V). NPY and POMC are expressed in discrete populations of arcuate nucleus neurons. NPY release in the PVN and LHA/PFA regions stimulates eating, whereas release of [alpha]-MSH (derived from POMC) in the PVN has an anorexic effect.

The hypothesis that the arcuate nucleus transduces information related to signalling by leptin into a neuronal response is supported by the anorexic response to local microinjection of leptin into this area [67](#), and the inability of i.c.v. leptin to reduce food intake after the arcuate nucleus has been destroyed [68,69](#). A majority of both NPY/AGRP and POMC/CART neurons have been found to coexpress leptin receptors [16,17](#) and both types of neurons are regulated by leptin (as judged by changes in neuropeptide gene expression), but in an opposing manner. Thus, NPY/AGRP neurons are inhibited by leptin, and consequently are activated in conditions where leptin levels are low [44,45,60,61](#). Although less well studied, a deficiency of insulin also seems to activate these neurons [20,47](#), and insulin receptors are highly concentrated in the arcuate nucleus [15](#). Conversely, conditions characterized by reduced insulin or leptin inhibit POMC [70,71](#) and CART [52](#) expression in the arcuate nucleus, and administration of these hormones can prevent or attenuate these neuropeptide responses. Moreover, involuntary overfeeding in rats, which potently inhibits spontaneous food intake once body weight has increased by more than 5%, elicits a threefold increase of POMC messenger RNA levels in the arcuate nucleus [72](#). The demonstration that anorexia induced either by leptin [73](#) or by involuntary overfeeding [72](#) is reversed by central administration of a melanocortin-receptor antagonist (at a low dose that has no effect on food intake in control animals) indicates that melanocortin signalling is a mediator of the anorexic response induced by increased adiposity signalling to the brain. Taken together, these findings indicate that the arcuate nucleus is a major site for transducing afferent input from circulating leptin and insulin into a neuronal response.

Implicit in this hypothesis is the suggestion that brain areas innervated by arcuate nucleus neurons are sites where second-order neurons involved in the energy homeostasis circuit are located. But the identification of such downstream neurons is just beginning, and energy homeostasis probably involves integrated and redundant pathways, rather than a discrete set

of neurons connected in series to one another. Models for understanding how arcuate nucleus neurons ultimately affect food intake nonetheless provide a useful framework for future study. One possible model is proposed below.

Model for second-order neuronal signalling pathways [↑](#)

Hypothalamic areas including the paraventricular nucleus (PVN), zona incerta, perifornical area (PFA) and LHA are richly supplied by axons from arcuate nucleus NPY/AGRP and POMC/CART neurons [74,75](#). Insight into the role in energy homeostasis played by neurons in these areas can be gleaned from earlier stimulation and lesioning studies. For example, PVN stimulation inhibits food intake, whereas the reverse is true of stimulation of the LHA [50](#) and adjacent PFA [76](#). Conversely, bilateral PVN lesions cause a hyperphagic obesity syndrome, whereas bilateral lesioning of the LHA causes anorexia and weight loss [50,64](#). These observations indicate that anorexigenic and orexigenic signalling molecules might be synthesized in the PVN and LHA, respectively ([Fig. 5](#)).

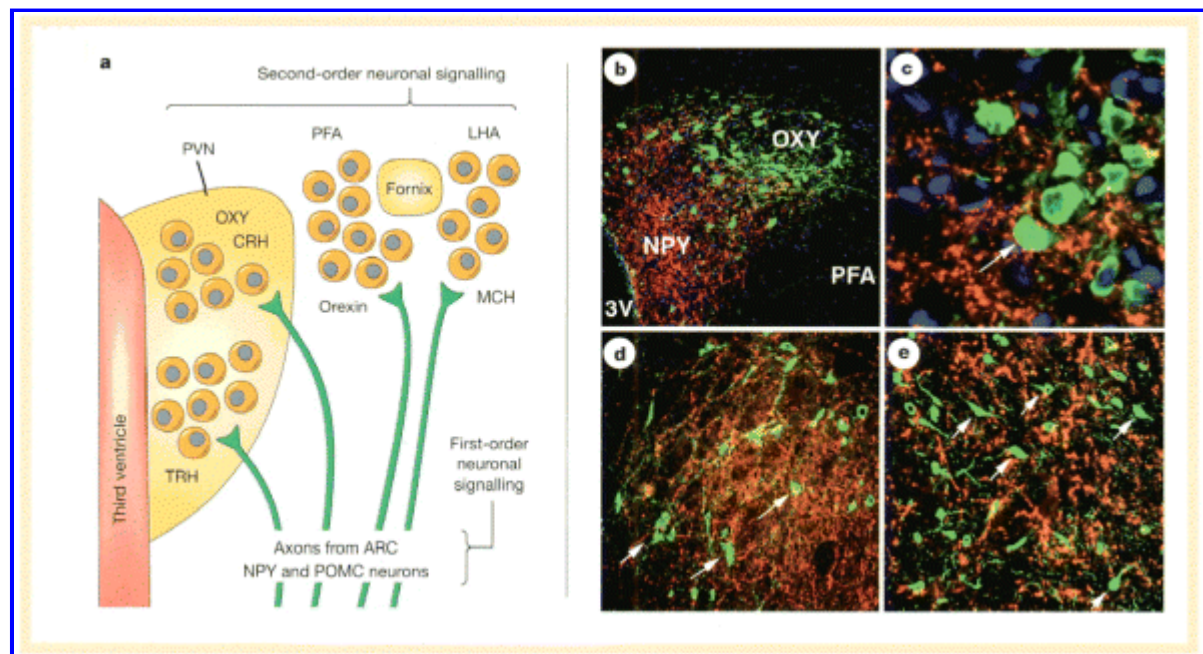


Figure 5 Locations of candidate second-order neurons involved in the hypothalamic response to insulin and leptin adiposity signalling. **a**, Diagram showing neuronal axons containing NPY and [alpha]-MSH from the arcuate nucleus (ARC) innervating the PVN, LHA and PFA (adjacent to the fornix). Candidate second-order neurons include those that express TRH, CRH and oxytocin (OXY) in the PVN (which cause anorexia), and neurons that express orexins and MCH in the PFA and LHA (which increase feeding). **b**, Fluorescence double-immunocytochemical staining of the PVN, showing NPY-containing axons (red fluorescence) in the parvocellular region adjacent to the third ventricle and magnocellular OXY neurons (green fluorescence) in the lateral PVN. The PFA is located lateral to the PVN, but the fornix and LHA are not included in this field. **c**, Higher magnification of OXY neurons (green fluorescence) surrounded by axons and terminals containing NPY (red fluorescence). Nuclei of cells are shown in blue fluorescence. **d**, PFA showing NPY-containing axons (red fluorescence) surrounding neuron cell bodies containing orexins (green fluorescence). **e**, LHA showing NPY-containing axons (red fluorescence) surrounding neuron cell bodies containing MCH (green fluorescence).

Consistent with these predictions, several neuropeptides synthesized in PVN neurons reduce food intake and body weight when administered centrally. These include CRH, which causes anorexia and also activates the sympathetic nervous system in addition to its role as a major regulator of the hypothalamic-pituitary-adrenal axis [50,77](#); TRH, which reduces food intake [51](#) in addition to stimulating the thyroid axis; and oxytocin, which reduces food intake in addition to regulating uterine function [78](#). If these PVN neurons are second-order catabolic effectors located downstream of the arcuate nucleus, they should be stimulated by melanocortin and/or CART signalling, but inhibited by NPY signalling, and further study is

warranted to test this prediction.

The hypothesis that second-order neurons involved in anabolic signalling reside within the LHA/PFA is supported by studies of MCH, an orexigenic peptide located in this brain area [79](#). Evidence that MCH synthesis is elevated by both energy restriction and leptin deficiency [79](#), and that MCH-knockout mice have reduced food intake and are excessively lean [80](#), is consistent with this model. The discovery of the MCH receptor as a G-protein-coupled receptor (previously known as SLC-1) [81,82](#) also supports the hypothesis of MCH as an orexigenic factor. Like NPY receptors, the MCH receptor is coupled to the G_i subunit of the plasma membrane G-protein assembly. By activating G_i , binding of MCH to its receptor inhibits formation of cyclic AMP and consequently reduces signalling by protein kinase A (PKA) [81,82](#). This effect is opposite to that mediated by activation of receptors that exert anorexic effects, such as MC4 or CRH receptors, which are coupled to G_s and consequently increase cAMP and PKA signalling.

Two additional peptides are expressed exclusively in the LHA, zona incerta and PFA. Termed 'hypocretins 1 and 2' [83](#) or 'orexins A and B' [84](#) by the two groups that simultaneously discovered them, these peptides increase food intake and cause generalized behavioural arousal when administered centrally [84,85](#). Targeted deletion of the hypocretin/orexin gene in mice induces narcolepsy [86](#), a disorder characterized by the sudden onset of sleep at times when it would not ordinarily occur. This finding indicates that reduced hypocretin/orexin signalling may contribute to the onset and maintenance of sleep, in addition to its potential role in the control of food intake. Integration of MCH and hypocretin/orexin neurons into a model of the hypothalamic pathways controlling energy homeostasis predicts that they should be inhibited by melanocortin or CART input, and stimulated by NPY signalling, from neurons of the arcuate nucleus.

Much work must be done to test this model of first- and second-order neurons in the energy homeostasis circuit. Identifying specific neuronal subsets in the PVN and LHA that express NPY and melanocortin receptors is an important priority. Because many neurons of the PVN, PFA and LHA project to the arcuate nucleus, neuronal traffic flows bidirectionally between the arcuate nucleus and these other hypothalamic sites. So rather than being passive recipients of information from the arcuate nucleus, these second-order neurons can actively modify the information that arrives there. In addition, leptin receptors have been described on PVN and LHA neurons, implicating them as direct targets for regulation by circulating adiposity signals. However, far greater concentrations of leptin receptors are present in the arcuate nucleus than in these other hypothalamic sites.

Satiety signals control meal size

It is self-evident that either the amount of food consumed during individual meals, the frequency of meals, or both, must be regulated if energy homeostasis is to be achieved. The major determinant of meal size is the onset of satiety, a biological state induced by neurohumoral stimuli generated during food ingestion that leads to meal termination. To clarify how the decision to terminate a meal once it has begun is controlled in the regulation of energy homeostasis, we propose that hypothalamic pathways involved in energy homeostasis interact with a distinctly different set of pathways involved in the response to satiety signals [65,87](#). In contrast to the timing of meal initiation, which can be influenced by many external and internal variables (for example, emotional factors, time of day, availability and palatability of foods, and threats from the environment), meal termination tends to be a more biologically controlled process [88](#). Several findings indicate that control of meal size is a component of the feeding response induced by changes of body fuel stores or adiposity signalling. The hyperphagic response to central administration of NPY, for example, arises predominantly from the consumption of larger meals [89](#). Conversely, leptin-treated animals

consume the same number of meals as vehicle-treated controls, but the meals are smaller [90](#). These observations indicate that signals involved in energy homeostasis may control food intake primarily by adjusting the size of individual meals. One way that this could be accomplished is by modulating the response to satiety signals in brain areas that process this information.

In contrast to its major role in mediating the response to adiposity signals, the hypothalamus is probably not the site that processes satiety signals. Rather, satiety information generated during the course of a meal is largely conveyed to the hindbrain by means of afferent fibres of the vagus nerve and by afferents passing into the spinal cord from the upper gastrointestinal tract [91](#). This information converges in the nucleus tractus solitarius (NTS), an area of the caudal brainstem that integrates sensory information from the gastrointestinal tract and abdominal viscera, as well as taste information from the oral cavity [92](#). Satiety-inducing signals that reach the NTS are initiated by mechanical or chemical stimulation of the stomach and small intestine during food ingestion, neural input related to energy metabolism in the liver [93](#) and humoral signals such as cholecystokinin (CCK) that are released upon nutrient stimulation of neuroendocrine secretory cells lining the intestinal lumen [94](#). Meal termination induced by such satiety signals can be demonstrated even when all neuronal connections between forebrain and hindbrain are severed [95](#). The basic process of terminating a meal, therefore, involves brain areas that can function in the absence of hypothalamic influences.

How then is the forebrain response to adiposity signals coupled to changes in the size of single meals? The hypothesis that such responses ultimately involve an interaction with hindbrain areas that control satiety is supported by the ability of both leptin [96](#) and insulin [87](#) to enhance the satiating effect of CCK. This interaction may be explained by the ability of central effector pathways to influence the response of NTS neurons to input from vagal afferents that convey satiety-related stimuli ([Fig. 6](#)). Recent evidence that leptin potentiates the effect of CCK to activate NTS neurons demonstrates clearly that signals involved in energy homeostasis modulate the response of NTS neurons to input related to satiety [97](#).

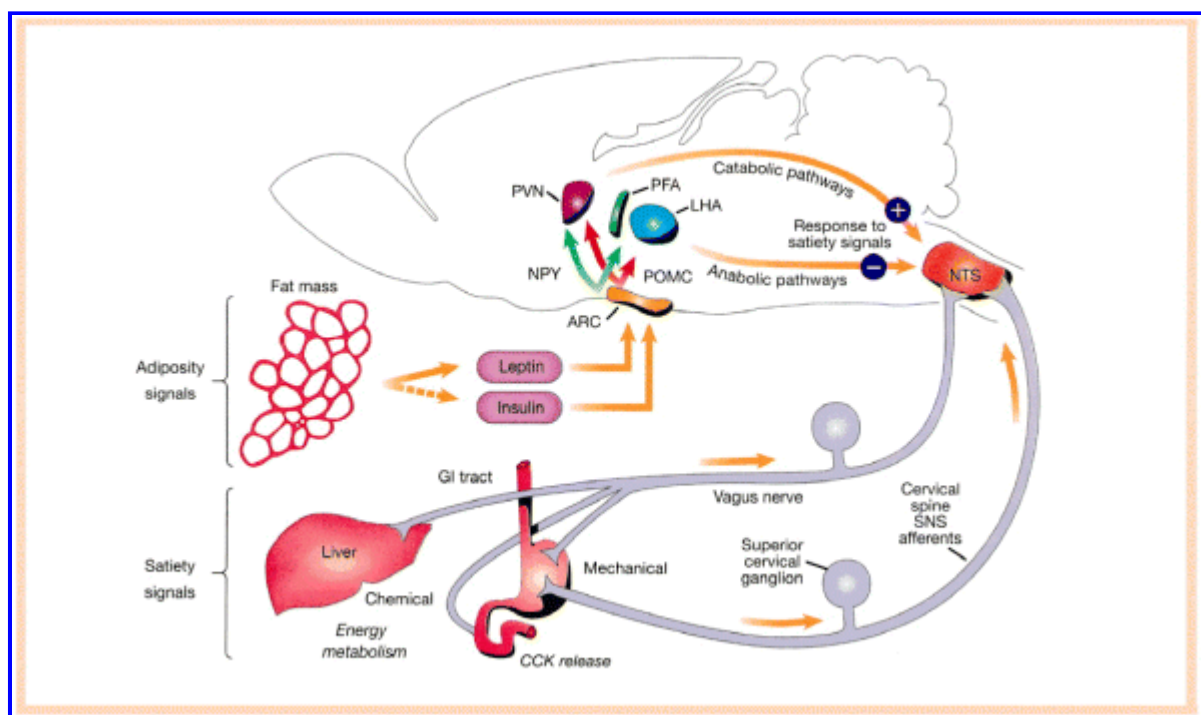


Figure 6 Neuroanatomical model of pathways by which adiposity signals, leptin (secreted by adipocytes) and insulin (secreted by the endocrine pancreas in proportion to adiposity), interact with central autonomic circuits regulating meal size. Leptin and insulin are proposed to stimulate a catabolic pathway (POMC/CART neurons) and inhibit an anabolic pathway

(NPY/AGRP neurons) that originates in the arcuate nucleus (ARC). These pathways project to the PVN and LHA/PFA, where they make connections with central autonomic pathways that project to hindbrain autonomic centres that process satiety signals. Afferent input related to satiety from the liver, gastrointestinal tract and from peptides such as CCK are transmitted through the vagus nerve and sympathetic fibres to the nucleus of the solitary tract (NTS), where they are integrated with descending hypothalamic input. Net neuronal output from the NTS and other hindbrain regions leads to the termination of individual meals, and is potentiated by catabolic projections from the PVN and inhibited by input from the LHA/PFA. Reduced input from adiposity signals (for example, during diet-induced weight loss), therefore, increases meal size by reducing brainstem responses to satiety signals. Not shown are ascending projections from hindbrain to forebrain that may also contribute to adaptive changes in food intake.

Several caveats follow as a result from the hypothesis that NTS neurons are themselves responsible for integrating afferent information related to satiety with descending inputs from forebrain neurons involved in energy homeostasis. First, NTS neurons have reciprocal interconnections with forebrain areas such as the PVN [98](#), so the integration of satiety and energy homeostasis information probably involves multiple brain areas. In addition, the neuronal substrates for responding to central effector peptides involved in energy homeostasis are present locally within the NTS, as well as in the hypothalamus. For example, MC4 receptors are expressed in the NTS [54](#), and local administration of MC4-receptor agonists or antagonists into the fourth ventricle (which is adjacent to the NTS) elicits feeding responses that are indistinguishable from those induced by injecting these compounds into the more rostral lateral ventricle [99](#). This finding, combined with evidence that leptin receptors [100](#) and POMC neurons are both present in the NTS (the only brain area other than the arcuate nucleus that expresses the POMC gene)[101](#), indicates that the hindbrain and forebrain may both process information involved in energy homeostasis. Thus, the NTS or other brainstem areas may, like the arcuate nucleus, contain neurons that respond to leptin and, through ascending projections to key forebrain sites, contribute to adaptive feeding responses to changes in body fat content. Further clarification of the mechanisms that integrate forebrain and hindbrain circuitry involved in this process is an important area for future study.

Monoamine neurotransmitters and food intake

Noradrenaline

Noradrenaline is synthesized in brainstem areas such as the dorsal vagal complex and the locus ceruleus. These areas project both caudally to the spinal cord and rostrally to the hypothalamus, thalamus and cortex. In some of these neurons, including those projecting to the PVN, noradrenaline is co-localized with NPY. Like NPY, injection of noradrenaline into the PVN increases food intake robustly and repeated injections can result in substantial weight gain [102](#). The observation of elevated noradrenaline levels in the PVN of *ob/ob* mice [103](#) indicates that leptin may inhibit noradrenaline release from terminals in this brain area, a possibility supported by *in vitro* studies using rat hypothalamus [104](#). Increased noradrenaline signalling in the PVN or other hypothalamic areas may therefore contribute to hyperphagia induced by leptin deficiency, a hypothesis that implicates noradrenaline as an anabolic effector in the CNS control of energy homeostasis.

Dopamine

A critical dependency of food intake on CNS dopamine signalling is implied by the profound feeding deficits that result from both pharmacological depletion [105](#) and genetic disruption [106](#) of dopamine synthesis. The interpretation of this finding is complicated, however, by motor impairments associated with dopamine deficiency that may also affect feeding behaviour. The observation that the feeding effects of dopamine vary with the brain region under study further obscures its role in energy homeostasis. For example, mesolimbic dopamine pathways (comprised of cell bodies in the substantia nigra and ventral tegmental area that project to the nucleus accumbens, striatum and cerebral cortex) seem to contribute

to the 'rewarding' aspects of consuming palatable foods [107](#). In contrast, dopamine signalling in the hypothalamus via neurons situated in the dorsomedial and arcuate nuclei seems to inhibit food intake. Although reduced dopamine levels in the arcuate nucleus of *ob/ob* mice [103](#) raise the possibility that decreased hypothalamic dopamine signalling contributes to hyperphagia induced by leptin deficiency, the finding that leptin inhibits dopamine release from rat hypothalamus *in vitro* [104](#) is inconsistent with this hypothesis.

Synaptic concentrations of neurotransmitters are determined not only by the rate of their release from nerve terminals, but also by their rate of removal from the synaptic cleft. The latter process is dependent on specific transporter proteins that mediate neurotransmitter reuptake, the expression of which can be influenced by metabolic and hormonal factors [108](#). For example, fasting and uncontrolled diabetes reduce synaptic dopamine reuptake (which increases synaptic dopamine levels) [109](#), whereas the reverse is true for noradrenaline [108](#). Because these effects are reversed by insulin infusion directly into the brain, they may be mediated, at least in part, by reduced CNS insulin signalling.

Serotonin [↑](#)

The serotonin system is comprised of cell bodies in the caudal brainstem including the dorsal raphe nuclei that project widely throughout the brain, and is the primary target of several centrally acting drugs developed for obesity treatment (for example, dexfenfluramine and sibutramine). Such drugs increase serotonin-receptor signalling and thereby suppress food intake, whereas antagonists have the opposite effect [110](#). The 5HT_{2C} serotonin-receptor subtype is implicated in this process, as knockout of this receptor increases food intake and body weight [11](#). Maintenance of normal energy homeostasis, therefore, seems to require intact serotonin signalling. But obesity in this model is modest, especially when compared to the phenotype of mice lacking MC4 or leptin receptors. The recent finding that leptin increases serotonin turnover [112](#) raises the possibility that at least some of leptin's weight-reducing effects are mediated through increased serotonin signalling. However, leptin-induced anorexia is intact in mice lacking the 5HT_{2C} receptor [111](#), indicating that leptin's ability to reduce food intake does not require signalling at this receptor subtype.

Aminergic neurotransmitter systems, therefore, exert unambiguous effects on food intake and provide important targets for current approaches to drug treatment of obesity. The role of these systems in energy homeostasis is complex, however, and the hypothesis that they serve as major targets for the action of adiposity signals is not strongly supported.

Therapeutic implications [↑](#)

A more detailed understanding of the pathogenesis of human obesity may ultimately guide treatment of affected individuals. Obesity that results from reduced melanocortins, for example, might respond well to administration of melanocortin-receptor agonists, if and when they become available in a clinical setting. Evidence for this is provided in a recent study of POMC-knockout mice, in which obesity was reversed by administration of an MC4-receptor agonist [113](#). Analogously, administering leptin to an obese human with genetic leptin deficiency reduced weight as markedly as it does in *ob/ob* mice [114](#). Obesity that is associated with leptin resistance, however, may be common and would be unlikely to respond to leptin treatment unless the resistance can be overcome. Patients with defective melanocortin-receptor function, for example, seem unlikely to respond to therapy with either leptin or melanocortin-receptor agonists. These considerations indicate that an expanded ability to diagnose the pathophysiological basis of human obesity will have direct applications to its treatment. However, a multidrug regimen that targets multiple sites within the weight-regulatory system may be necessary to achieve and sustain weight loss in many individuals.

The impressive effects of AGRP on food intake in rodents [62,63](#) indicate that it warrants evaluation in the treatment of conditions associated with excessive weight loss, including anorexia nervosa and wasting illness associated with AIDS or cancer. If AGRP proves ineffective in this context, it would indicate that the pathogenesis of such conditions involves pathways additional to, and potentially downstream of, melanocortin-receptor activation. Such an outcome might therefore direct therapeutic strategies towards activation of other candidate anabolic (or inhibition of catabolic) effector pathways.

These considerations highlight the importance of clarifying the mechanisms that control food intake and energy homeostasis. Such information will help us to understand the pathogenesis of disorders at both ends of the body-weight spectrum, and is a probable prerequisite for their successful treatment. The enormous cost to human health attributable to these disorders emphasizes the need for a more complete understanding of this area.

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