Central Nervous System Control of Food Intake and body Weight

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Central nervous system control of food intake and body weight

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The capacity to adjust food intake in response to changing energy requirements is essential for survival. Recent progress has provided an insight into the molecular, cellular and behavioural mechanisms that link changes of body fat stores to adaptive adjustments of feeding behaviour. The physiological importance of this homeostatic control system is highlighted by the severe obesity that results from dysfunction of any of several of its key components. This new information provides a biological context within which to consider the global obesity epidemic and identifies numerous potential avenues for therapeutic intervention and future research.

The apparent ease with which we decide whether or not to eat an appetizing food testifies to the efficiency with which the central nervous system (CNS) processes information of surprising variety and complexity. With the aid of cognitive, visual and olfactory cues, food items must first be identified and distinguished from a nearly infinite array of potentially toxic environmental constituents. Using taste information, the food's palatability is then assessed and integrated with both short- and long-term signals regarding nutritional state. One consequence of this integration is that the drive to eat decreases as food is ingested (termed 'satiation'), ensuring that the amount consumed in a single meal does not exceed what the body can safely handle. Changing energy requirements is another factor that can influence food consumption. Through a process known as energy homeostasis, food intake is adjusted over time so as to promote stability in the amount of body fuel stored as fat. In this way, through diverse blood-borne and afferent neural signals, information regarding nutrient status and energy stores is communicated to the brain where it is integrated with cognitive, visual, olfactory and taste cues—all happening unconsciously, before the first bite is taken.

Here we describe CNS mechanisms that regulate food intake, and review evidence that in response to reduced body fat stores, adaptive changes occur in neuronal systems governing both food-seeking behaviour (important for meal initiation) and satiety perception (important for meal termination). The net effect is that in response to weight loss, both the motivation to find food and the size of individual meals tend to increase until energy stores are replenished (Fig. 1), and mutation of any of several key molecules involved in this process has been shown to cause severe obesity in both animal models and humans. Despite this progress, the many fundamental questions remaining unanswered represent rich opportunities for future study.

Energy homeostasis

Obesity, by definition, results from ingesting calories in excess of ongoing requirements. Although environmental and lifestyle factors contribute to obesity pathogenesis, homeostatic adaptations to weight loss induced by voluntary caloric restriction are robust in both lean and obese individuals. In addition, normal-weight individuals are protected against expansion of body fat stores induced by overfeeding[1,2], indicating that biological mechanisms protect against weight gain as well as weight loss, at least in normal-weight individuals. Together, these findings indicate that obesity involves the defence of an elevated body weight, rather than the absence of regulation, and that deleterious interactions between obesity-promoting environmental factors and homeostatic control systems contribute to common forms of obesity and, hence, the global obesity pandemic.

Adiposity negative feedback. Introduced more than 50 years ago, the 'adiposity negative-feedback' model of energy homeostasis is founded on the premise that circulating signals inform the brain of changes in body fat mass and that in response to this input, the brain mounts adaptive adjustments of energy balance to stabilize fat stores[3]. Proposed criteria for a negative-feedback signal include: (1) that it circulates at levels proportionate to body fat content and enters the brain; (2) that it promotes weight loss by acting on neuronal systems implicated in energy homeostasis; and (3) that blockade of these neuronal actions increases food intake and body weight. Although many nutrients (for example, free fatty acids and glucose), cytokines (for example, interleukin-6, tumour necrosis factor-α) and hormones (for example, glucocorticoids) fulfill some of these criteria, only leptin and insulin satisfy all of them[4].

Studies in primitive organisms such as the nematode, *Caenorhabditis elegans*, and the fruitfly, *Drosophila melanogaster*, implicate insulin as a key ancestral negative-feedback regulator of body fuel stores[5,6]. By comparison, leptin has not been detected in invertebrates and probably evolved more recently[7]. Although genetic and pharmacological studies[8,9] suggest a more critical role for leptin than insulin in mammalian energy homeostasis, cross-talk between these hormones with respect to both the neuronal subsets and signal transduction pathways on which they act offers evidence of their shared evolutionary past.

Although leptin administration causes weight loss in diverse mammalian species, enthusiasm surrounding leptin as a therapeutic agent diminished rapidly with the discovery that leptin resistance is common among obese individuals[10]. Because obesity has long been associated with insulin resistance in peripheral tissues, it is perhaps not surprising that in obese rats, the hypothalamus develops resistance to insulin[11] as well as leptin[12]. Although reduced neuronal signalling by either hormone induces hyperphagia and weight gain

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in animal models[13,14], whether neuronal resistance to these hormones contributes to the pathogenesis of common obesity is an important unanswered question.

Gastrointestinal hormones. Peptide YY$_{3-36}$ (PYY$_{3-36}$) is an enteric hormone that can reduce food intake in rodents and humans[15]. Whereas plasma levels of PYY$_{3-36}$ decline in advance of meals, levels of the gastric hormone ghrelin rise shortly before meals and fall sharply on feeding[16]. Opposing the hypothalamic actions of leptin, insulin and PYY$_{3-36}$, ghrelin powerfully stimulates food intake in multiple species, including humans[17–19], suggesting that the effect of weight loss to increase ghrelin levels[20] may (along with reduced leptin and insulin levels) contribute to weight regain.

Nutrient-related signals. In addition to molecular targets of current anti-obesity drugs, including receptors for endocannabinoids, nor-epinephrine and serotonin[21–23], several nutrient-related signals are implicated in the homeostatic control of feeding. Among these are free fatty acids, which exert insulin-like effects in key brain areas for energy homeostasis, including the hypothalamic arcuate nucleus (ARC), possibly by favouring intracellular accumulation of long-chain fatty acyl-CoA (LCFA-CoA)[24,25]. The hypothesis that hypothalamic LCFA-CoA signalling has a critical role in energy homeostasis is supported by the obesity that results when the level of these molecules is selectively reduced in rat ARC[26].

Whereas intracellular LCFA-CoA accumulation is proposed to signal nutrient abundance, the enzyme AMP-activated protein kinase (AMPK) is a sensor of nutrient insufficiency. When cells experience a critical drop of fuel availability (as reflected by an increased AMP/ATP ratio), AMPK activation increases substrate oxidation to replenish depleted ATP levels. In mediobasal hypothalamus, activation of AMPK increases food intake and body weight whereas conversely, inhibition of AMPK has the opposite effect[27]. Because hypothalamic AMPK activity is inhibited by leptin and insulin[27], but stimulated by ghrelin[28], altered AMPK signalling may contribute to the feeding effects of these hormones. One consequence of increased AMPK activity is oxidation of LCFA-CoA, and this mechanism might contribute to its orexigenic effects. AMPK also decreases the activity of another nutrient-sensing enzyme, mammalian target of rapamycin (mTOR), implicated in hypothalamic leptin action[29].

Regulation of satiety perception

Most vertebrates consume food in discrete bouts or 'meals'. Although numerous environmental variables can influence meal initiation, satiety perception is a more biologically determined and predictable process[30], triggered on nutrient ingestion by gastric distension and the release of gut factors including cholecystokinin (CCK)[31]. Many such 'satiety signals' are transmitted to the brain via vagal afferent fibres that synapse in the nucleus tractus solitarius (NTS) in the hindbrain, which participates in gustatory, satiety and visceral sensation.

Because homeostatic adjustments of food consumption must, by definition, involve changes of meal size, meal frequency, or both, systems that control energy homeostasis must integrate with those governing intake on a meal-to-meal basis. In rats, leptin reduces intake, at least in part, by enhancing the response to satiety signals[32], whereas conversely, obese, leptin-receptor-deficient rats exhibit blunted satiety responses to CCK, and this defect is ameliorated by restoring leptin receptors to the ARC[33]. This result suggests that in response to afferent input from leptin, homeostatic circuits in the hypothalamus elicit compensatory reductions of food intake by enhancing the response to meal-related satiety signals. Brain areas beyond the ARC also probably contribute to leptin's enhancement of the response to satiety signals, because leptin receptors are present in many brain areas involved in food intake control, including the NTS itself[34,35], and because leptin administration directly into the NTS reduces food intake[34]. The integration of long-acting homeostatic and short-acting satiety signals may therefore involve direct actions of leptin on NTS neurons that process input from vagal afferent fibres, in addition to its effects on neurons in hypothalamus and elsewhere that project to the NTS (Fig. 2)[36].

Mechanisms of food reward

Perception of food reward begins with information generated by oral taste receptor cells that is subsequently transmitted to the NTS by afferent sensory fibres. From the NTS, taste information is conveyed to multiple sites in the hindbrain (for example, parabrachial nucleus), midbrain (ventral tegmental area or VTA) and forebrain (for example, nucleus accumbens (NAc), striatum, thalamus and cerebral cortex)[37], which collectively sense and discriminate among
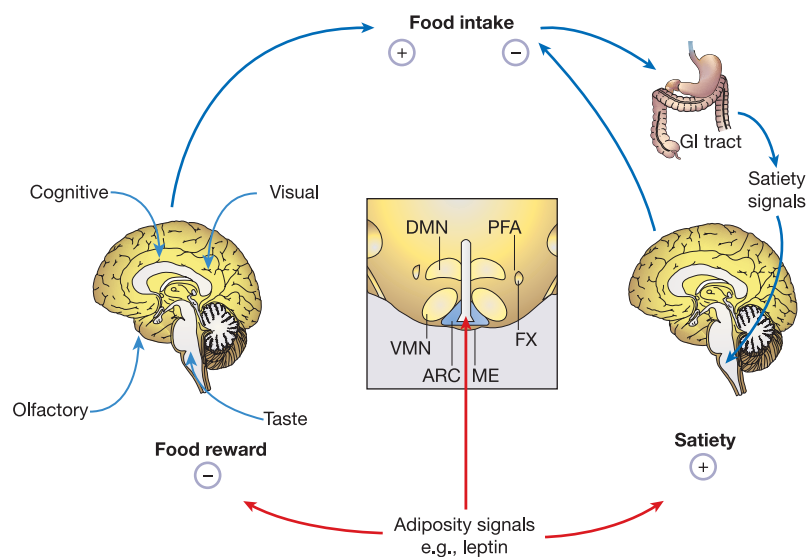

Figure 1 | Model for negative-feedback regulation of food intake in response to changes in body fat content. Hormones such as leptin circulate in proportion to body fat mass, enter the brain, and act on neurocircuits that govern food intake. Through both direct and indirect actions, leptin diminishes perception of food reward—the palatability of food—while enhancing the response to satiety signals generated during food consumption that inhibit feeding and lead to meal termination. The effect of weight loss to lower leptin levels (and hence to reduce leptin signalling) increases rewarding properties of food while diminishing satiety, a combination that potently increases intake. ARC, arcuate nucleus (highlighted in blue); DMN, dorsomedial nucleus; FX, fornix; ME, median eminence; PFA, perifornical area; VMN, ventromedial nucleus.

different tastes and textures, assigning reward value to them (Fig. 3). Higher processing of taste information in primates involves 'primary taste neurons' in the insular cortex that are supplied by NTS neurons by way of the thalamus. These cells project in turn to 'secondary taste neurons' in the orbitofrontal cortex that integrate taste information with relevant olfactory, visual and cognitive inputs[38]. The response of these latter cells (but not of primary taste neurons) to taste stimuli is described as 'hunger-dependent', in that it decreases as food is eaten, implying the capacity to integrate taste information with satiety-related (and perhaps adiposity-related) input[38]; data obtained using functional magnetic resonance imaging in humans support this view[39]. According to this hypothesis, reduced firing of secondary taste neurons diminishes the reward value of foods and thereby contributes to meal termination via projections to the striatum and amygdala, areas that attach motivational value needed to engage motor outputs[39]. Whether activity of secondary taste neurons in the orbitofrontal cortex is sensitive to input from adiposity and satiety signals, and whether it is either necessary or sufficient to explain hedonic stimulation of feeding behaviour, are questions that warrant further study.

Reward valuation involves the release of dopamine from neurons that originate in the VTA and project to NAc, striatum and other brain areas[37,40]. Acting in these forebrain areas, dopamine potently augments the drive to obtain a rewarding stimulus (that is, increases the 'wanting' of a particular food or drug)[40], but it is not directly responsible for the hedonic experience itself (that is, the 'liking' of a palatable food). Rather, μ-opioid receptor signalling in the NAc and adjacent forebrain structures (activated in part by dopamine release) is implicated in the hedonic experience[37,40], although wanting and liking ordinarily occur together.

One mechanism whereby activation of the VTA → NAc pathway may promote consumption of palatable food involves projections to the lateral hypothalamic area. This brain area contains neurons that potently stimulate food intake and is supplied by fibres not only from striatum and orbitofrontal cortex, but also from the ARC
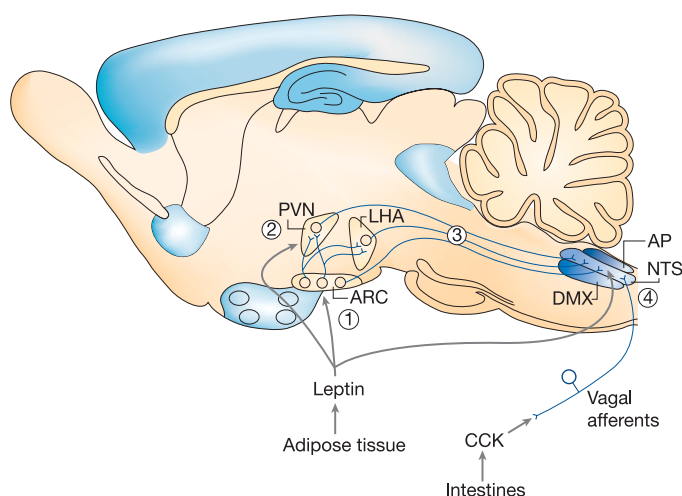
and other crucial hypothalamic areas for energy homeostasis. Food-intake-stimulatory neurons in the lateral hypothalamic area seem to be constrained by tonic inhibition that can be relieved by activation of reward pathways, thereby engaging motor programs that stimulate feeding behaviour[37]. Lateral hypothalamic area neurons supplying the NTS may, in addition, attenuate the response to satiety signals, increasing the amount of food consumed during a meal. These considerations support a view of the lateral hypothalamic area as an integrative node for homeostatic, satiety and reward-related inputs that collectively govern motor programs that activate feeding behaviour (Fig. 3).

Regulation of brain reward circuitry

The concept that reward perception is subject to homeostatic regulation derives from evidence that food deprivation strongly augments the reward value (for example, the speed of learning to obtain a rewarding stimulus, the dose of the stimulus needed to establish its rewarding value, or the amount of work an animal will perform to obtain the stimulus) of addictive drugs including heroin, amphetamine and cocaine[41,42]. As fasting also augments the reinforcing value of electrical stimulation of brain 'pleasure centres'[43], reduced food availability seems to exert a global, stimulatory effect on reward perception. One mechanism to explain this effect proposes that leptin and insulin tonically inhibit brain reward circuitry and that, by lowering circulating levels of these hormones,
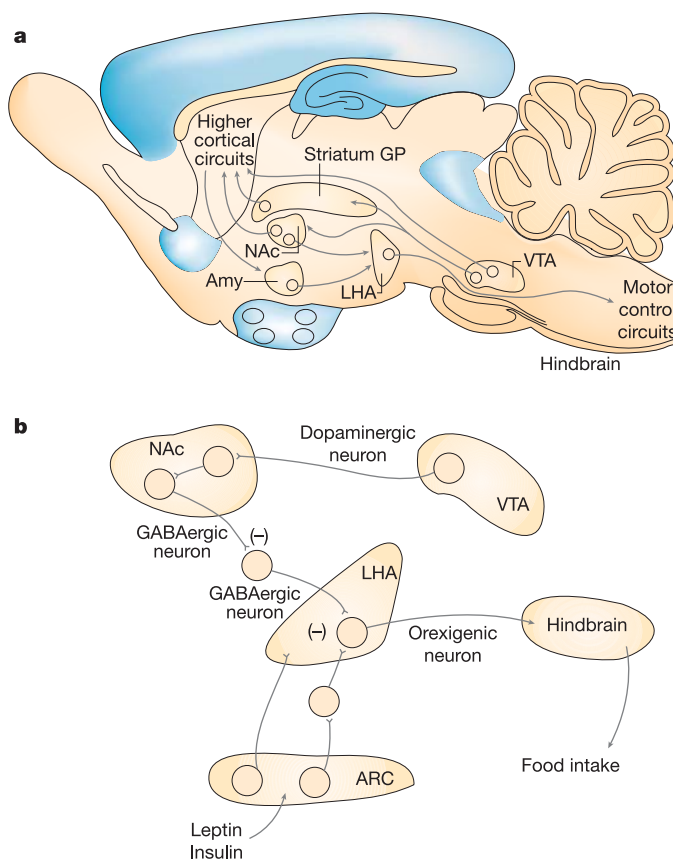
Figure 2 | Model for integration of adiposity- and satiety-related inputs. Afferent input in proportion to body fat mass (for example, leptin) enhances the response to satiety signals such as CCK that are generated in response to food consumption and lead to meal termination. Whereas the hypothalamus is a key target for leptin action, the satiety effect of CCK involves activation of vagal afferent fibres that terminate in the NTS. Integration of these inputs can involve the actions of leptin in the ARC (1) or other hypothalamic areas (2) involving neurons that project to the NTS (3) and influence the response to CCK (4). In addition, leptin can act directly in the NTS. AP, area postrema; DMX, dorsal motor nucleus of the vagus nerve; LHA, lateral hypothalamic area; NTS, nucleus of the solitary tract; PVN, paraventricular nucleus.

Figure 3 | Model for integration of adiposity- and reward-related inputs. Brain reward circuitry. **a**, Neurons in the VTA of the midbrain project to forebrain areas including the NAc, striatum and cortex, and assign reward value to palatable food. **b**, Perception of pleasure associated with consumption of a palatable food involves neuronal activation in the NAc and striatum, which through activation of opiate peptide receptors disinhibits the lateral hypothalamic area and thereby stimulates feeding. Amy, amygdala; GP, globus pallidus; NAc, nucleus accumbens; VTA, ventral tegmental area.

energy restriction increases the sensitivity of reward circuits[43,44]. Consistent with this hypothesis, centrally administered insulin or leptin diminishes both sucrose preference (a measure of food reward)[44] and the effect of fasting to increase the rewarding properties of electrical pleasure-centre stimulation[43]. At the cellular level, increased expression of dopamine re-uptake transporters in VTA neurons, which reduces synaptic dopamine levels in the NAc[45], may contribute to the inhibitory effect of adiposity-related hormones on food reward. Collectively, these observations suggest that by decreasing neuronal input from adiposity signals, energy restriction increases responses to rewarding stimuli as an adaptive mechanism motivating animals threatened by caloric insufficiency to seek and obtain palatable foods.

Neuronal sensing of adiposity-related signals

Recent studies have yielded testable, molecular models[46] to investigate how adiposity signals regulate the function of hypothalamic neurons. Like the ARC, the hypothalamic ventromedial nucleus was recently been shown to be essential for leptin regulation of energy balance[47], and identifying leptin-sensitive neurons in this area has become a high priority. Meanwhile, substantial progress has been made towards understanding how ARC neurons participate in this process. Among insulin- and leptin-sensing ARC neurons are those that co-express neuropeptide Y (NPY) and agouti-related protein (AgRP), neuropeptides that stimulate food intake via distinct mechanisms. These NPY/AgRP neurons are inhibited by leptin, insulin and PYY$_{3-36}$, whereas they are stimulated by ghrelin[46]. Consequently, weight loss activates these neurons through a combination of reduced inhibitory and increased stimulatory input[46] (Fig. 4a). Adjacent to these cells are neurons that express pro-opiomelanocortin (POMC), the polypeptide precursor from which melanocortins such as α-melanocyte stimulating hormone (α-MSH) are derived. On release from axon terminals, α-MSH binds to and activates neuronal melanocortin receptors, thereby decreasing food intake and favouring weight loss[48]. POMC neurons are stimulated by leptin[49] but inhibited by neighbouring NPY/AgRP neurons[49]. In response to

weight loss, activation of NPY/AgRP neurons is coupled to inhibition of POMC neurons, a combination that favours the recovery of lost weight and reflects the integration of diverse humoral and neuronal inputs[46].

Numerous observations support this model of how energy homeostasis circuitry is organized and regulated. For example, absence of leptin in obese (Lep^{ob}/Lep^{ob}) mice reduces *Pomc* expression in the ARC[50] while increasing levels of NPY and AgRP[4,51], mimicking the hypothalamic response to starvation. Similarly, absence of α-MSH in *Pomc* knockout mice causes hyperphagia and obesity[52], and blockade of neuronal melanocortin signalling diminishes the response to central leptin administration[53]. By comparison, deletion of *Npy*, *Agrp*, or both genes causes only mild defects in energy balance[54,55], raising questions about the relative importance of orexigenic versus anorexigenic signals in food intake and body weight regulation.

An oft-cited explanation for when knockout genotypes fail to yield abnormal phenotypes is 'genetic redundancy', in which loss of one gene is somehow compensated by altered expression of other genes or through more complex homeostatic mechanisms. How, then, are we to interpret the mild phenotype observed in mice lacking NPY and AgRP? To answer this question, investigators have recently ablated NPY/AgRP neurons themselves (rather than the genes encoding *Npy* and *Agrp*). Notably, the outcome of these studies depends on both the age of the animal and the time course over which the ablation occurs. In two studies, rapid ablation was accomplished by expressing the human receptor for diphtheria toxin selectively in NPY/AgRP neurons and injecting those animals with diphtheria toxin. (Humans have a gene that encodes a receptor for diphtheria toxin but mice do not; thus administration of low doses of diphtheria toxin to mice is normally harmless.) Using this approach, rapid ablation of NPY/AgRP neurons induced profound, life-threatening anorexia in adult mice[56,57], but not in mice in which these neurons were ablated during the neonatal period[56]. By contrast, gradual ablation over a period of months—brought about either by expressing a polyglutamine-containing protein[58] or by removing the capacity for oxidative
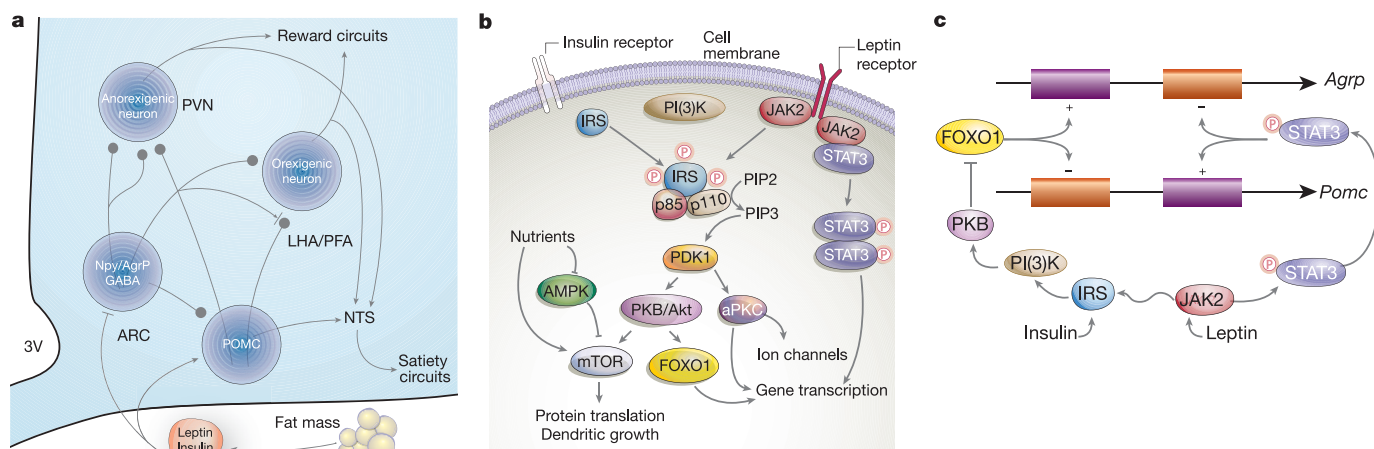

Figure 4 | Hypothalamic neurocircuits and signal transduction mechanisms involved in energy homeostasis. a, The arcuate nucleus (ARC) contains both NPY/AgRP neurons, which are inhibited by insulin and leptin and, when activated, stimulate food intake, and POMC neurons, which reduce food intake and are stimulated by insulin and leptin. Both neuronal subsets project to adjacent hypothalamic areas including the paraventricular nucleus (PVN), where neurons that reduce food intake are concentrated (anorexigenic), and the lateral hypothalamic area (LHA), which contains neurons that stimulate food intake (orexigenic). Outflow from each of these hypothalamic nuclei supplies 'downstream' brain areas involved in the perception of satiety (including the nucleus of the solitary tract (NTS) in the hindbrain) as well as food reward. NPY/AgRP neurons also inhibit POMC

neurons via synaptic release of the inhibitory transmitter, GABA (γ-aminobutyric acid). 3V, third cerebral ventricle; PFA, perifornical area. **b**, On binding to their respective receptors, both insulin and leptin activate the IRS–PI(3)K pathway. Phosphorylation of IRS proteins on tyrosine residues is induced by both the insulin receptor and by JAK2, a tyrosine kinase coupled to the leptin receptor, and allows IRS proteins to activate PI(3)K. By converting PIP2 to PIP3, PI(3)K activates PDK1, which in turn activates downstream enzyme systems including PKB and atypical PKC. Leptin receptor activation of JAK2 also induces tyrosine phosphorylation of STAT3, which dimerizes to become a transcription factor. **c**, Model for reciprocal regulation of *Pomc* and *Agrp* gene transcription via FOXO1 (which is inhibited by PKB) and STAT3 (modified from ref. 67).

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phosphorylation specifically in NPY/AgRP neurons[59]—had only mild effects on energy balance. Thus, orexigenic signals from these neurons have a critical role in body weight regulation, but if loss of these cells occurs early in life or via a gradual, progressive process, survival is ensured by as-yet-unidentified compensatory mechanisms.

What kinds of molecular and cellular mechanisms might underlie homeostatic compensation for NPY/AgRP neurodegeneration? An intriguing indication comes from studies using ciliary neurotrophic factor, which activates many of the same downstream signalling molecules as leptin, but which is not subject to neuronal resistance seen with leptin in obese models[60]. Surprisingly, ciliary neurotrophic factor stimulates proliferation of leptin-responsive neurons in the ARC[61], an intervention that may alter fundamentally the balance of orexigenic versus anorexigenic pathways in adult animals and thereby combat leptin resistance that accompanies obesity.

Signal transduction in ARC neurons. On insulin binding, the insulin receptor recruits several intracellular molecules involved in signal transduction[62]. Among these are insulin receptor substrate (IRS) proteins, which are phosphorylated on tyrosine residues by the activated insulin receptor. This, in turn, allows IRS proteins to activate phosphatidylinositol-3-OH kinase (PI(3)K), which generates phosphatidylinositol-3,4,5-trisphosphate (PIP3) from phosphatidyl-inositol-4,5-bisphosphate (PIP2). PIP3-mediated activation of PDK1 activates an enzyme cascade that includes protein kinase B (PKB, also known as Akt) and members of the atypical PKC family[62]. Among the targets of activated PKB are mTOR and the transcription factor FOXO1, which is inhibited by PKB-mediated phosphorylation (Fig. 4b).

The leptin receptor is a class 1 cytokine receptor that regulates gene transcription via activation of the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway. Leptin binding to the 'long' or 'signalling' form of the leptin receptor (LeprB) stimulates the tyrosine kinase JAK2 to phosphorylate STAT3 at tyrosine residues[63]. Phospho-STAT3 dimers subsequently enter the nucleus and regulate transcription of target genes. In some cells, including hypothalamic neurons[64], leptin also activates the IRS–PI(3)K pathway[65], one of several points of convergence and synergism between intracellular signalling pathways used by insulin and leptin. Together with evidence that hypothalamic IRS–PI(3)K signalling is increased by both hormones[65,66], convergent actions of leptin and insulin involving PI(3)K and STAT3 activation are proposed to regulate key energy homeostasis neurocircuits.

Recent analysis of transcriptional regulation of ARC neuropeptides by insulin and leptin supports this view. Consensus DNA binding sequences for both FOXO1 (a transcription factor that is inhibited by PI(3)K) and STAT3 exist close to one another in both *Agrp* and *Pomc* promoters, and the effect of STAT3 on transcription of both neuropeptide genes is opposite to that of FOXO1[67]. Thus, PI(3)K activation in response to insulin is proposed to inhibit FOXO1-mediated gene transcription. This response complements the effect of leptin-mediated STAT3 activation and provides a feasible explanation for how, during weight loss or other conditions of low plasma insulin and leptin levels, hypothalamic AgRP expression increases while POMC levels decline (Fig. 4c).

To understand better how ARC are regulated by insulin, leptin and other inputs, several groups have sought to measure membrane potential and firing rate, in addition to expression of neuropeptide genes. The hypothesis that PI(3)K signalling links input from insulin and leptin to changes of electrical activity in ARC neurons received early, direct support. Specifically, both hormones were reported to activate ATP-sensitive potassium (K$_{ATP}$) channels and thereby hyperpolarize a subset of 'glucose-responsive' ARC neurons via a PI(3)K-dependent mechanism[68]. These K$_{ATP}$ channels have subsequently emerged as key cellular targets for the actions of free fatty acids and other nutrient-related signals in the ARC. However, recent work suggests that although both insulin and

leptin activate PI(3)K signalling in arcuate POMC cells[64], the depolarizing effect of leptin on these cells[49,69] is reportedly opposed by a hyperpolarizing action of insulin[69]. Thus, PI(3)K signalling does not provide a unifying explanation for how these hormones affect POMC neuron firing rate and, moreover, insulin and leptin evidently have dissimilar effects on this parameter, despite their convergent effects to stimulate *Pomc* gene transcription[67].

As expected, leptin inhibits electrical activity of NPY/AgRP neurons[69,70], but whereas insulin increases PI(3)K signalling in these cells, leptin has the opposite effect[64]. The observation that leptin increases PI(3)K activity and firing rate in POMC neurons while inhibiting both parameters in NPY/AgRP neurons supports a causal link between leptin regulation of PI(3)K and neuronal activity, but this link does not hold for insulin. Whether and how PI(3)K activation affects neuronal firing, therefore, seems to vary with both the cell type and hormonal stimulus. In this context, the recent finding that leptin activates the nutrient-sensing enzyme mTOR in ARC neurons[29] is of interest. Because central inhibition of mTOR blocks leptin-mediated food intake suppression[29], mTOR activity seems to be essential for leptin action in this brain area. Yet, whereas mTOR is not implicated in the control of neuronal firing, it is a key determinant of dendritic growth and synaptic plasticity[71]. Because mTOR activation is well documented in response to both nutrient-related and IRS–PI(3)K signalling (Fig. 4b), it is possible that, rather than serving to link input from adiposity signals to firing rate, PI(3)K signalling in some hypothalamic neurons influences dendritic growth and synaptic input.

To clarify the involvement of specific molecules in ARC neurons *in vivo*, mice have been created in which IRS-2 (ref. 69), STAT3 or leptin receptor[72] is selectively deleted from POMC cells. The mild or absent obesity phenotype of these animals contrasts sharply with the severe obesity that results from *Pomc* gene deletion[52]. A logical interpretation of these findings is that, although neuronal melanocortin signalling is critical for energy homeostasis, neither leptin receptor → JAK–STAT nor IRS–PI(3)K signalling is essential for proper functioning of these cells. However, an alternative explanation is suggested by evidence that NPY/AgRP neurons exert a tonic inhibitory effect on neighbouring POMC cells[49], and that these two neuronal subsets are regulated in a reciprocal manner by many of the same afferent inputs (Fig. 4a). Nonlinearity in the relationship between the regulation of ARC neurons and their effects on food intake is illustrated through the following predictions that incorporate this arrangement. Mice with POMC-cell-specific deletion of the leptin receptor can be expected to exhibit reduced basal POMC neuron activity, creating a leptin-resistant state and increasing food intake. As weight is gained, rising plasma levels of leptin and insulin should subsequently inhibit NPY/AgRP neurons, which, in turn, will relieve tonic constraint of POMC cells. Through this mechanism the consequences of a reduced leptin signalling on POMC cells are mitigated and further weight gain limited.

These considerations highlight how the integrated, nonlinear nature of energy homeostasis neurocircuitry can complicate the interpretation of seemingly straightforward experiments. As the list of neuronal cell types and signal transduction molecules involved in energy homeostasis continues to expand, a 'systems biology' approach will help to more accurately model outcomes when molecules are deleted in a cell-specific manner.

Synaptic plasticity

Arcuate neurons are regulated not only by humoral signals but also by local excitatory and inhibitory synapses, and the balance of these inputs seems to be affected by nutritional state. Specifically, fasting decreases excitatory, while increasing inhibitory, synaptic contacts on POMC neurons, whereas the opposite applies for NPY/AgRP neurons[73]. Although the mechanism mediating these effects is unknown, it seems to involve the effect of fasting to lower leptin levels, as leptin-deficient mice display a similar alteration of synaptic

input. In addition, an unidentified subset of mediobasal ventro-medial nucleus neurons provides excitatory synaptic input to POMC cells, the magnitude of which is also attenuated by fasting[74]. Clarifying the extent to which synaptic regulation of hypothalamic neurons can influence the defended level of body adiposity, determining whether diet-induced obesity involves changes of brain circuitry at the synaptic level, and delineating the mechanisms underlying such effects are important scientific priorities. Realizing these goals requires new strategies for single-cell imaging, analysis of synaptic function, and modelling how synaptic changes affect energy homeostasis neurocircuitry and, consequently, the defended level of body weight.

Concluding remarks

Theoretically, drugs that target neuronal receptors for leptin, insulin, ghrelin, melanocortins, NPY or other relevant ligands have important potential, but hoped-for therapeutic breakthroughs have yet to emerge. Although delays between basic discovery and therapeutic application are inevitable, two obstacles that lie along this path are noteworthy. One of these is the integrated nature of energy homeostasis neuronal systems, which predicts that the efficacy of interventions targeting one neuronal subset or signal transduction pathway is inherently limited by compensatory responses elsewhere. As for many other chronic illnesses, effective prevention or treatment of obesity may therefore require drug combinations that target discrete components of energy homeostasis, satiety or food reward systems. However, drug combinations cannot be approved by the US Food and Drug Administration unless the drugs are individually proven safe and effective. Consequently, pharmaceutical companies have little incentive to pursue strategies involving drug combinations unless each of the drugs under consideration is, by itself, 'approvable'. This creates a situation in which potentially promising drug combinations are not developed because of limited efficacy of individual drugs when used alone.

Another obstacle arises from a lack of scientific consensus regarding fundamental aspects of obesity pathogenesis. During caloric restriction, there is little question that reduced neuronal input from adiposity-related hormones activates responses (increased food intake, decreased metabolic rate) that favour recovery of lost weight. Whether the reverse is also true—that increased neuronal input from these hormones protects against weight gain—is hotly debated. Until this issue is resolved, the importance of several key observations, including CNS resistance to leptin[12] and insulin[11] documented in common forms of obesity, will remain uncertain. This is because if adiposity negative-feedback signals do not normally protect against weight gain, neuronal resistance to insulin and leptin cannot cause obesity. According to this view, the growing obesity epidemic can be attributed to an inherent lack of protection against obesity-promoting environmental factors[75], rather than to an underlying homeostatic disorder. Alternatively, if adiposity negative-feedback signals do, in fact, confer protection against obesity in normal-weight individuals, neuronal resistance to these signals must, by definition, favour weight gain, and unravelling the underlying causes takes on both pathophysiological and therapeutic urgency. As our understanding of normal and abnormal regulation of food intake and body adiposity grows in its sophistication, overcoming these obstacles will create new opportunities for therapeutic intervention.

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