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Central regulation of energy balance: inputs, outputs and leptin resistance

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The regulation of energy balance is complex and, in man, imprecise. Nevertheless, in many individuals intake and expenditure are balanced with <1 % error with little or no conscious effect. Essential components of such a regulatory system are signals, leptin and insulin, that reflect the size of lipid stores. Leptin receptors signal via phosphatidylinositol 3-kinase (as do insulin receptors) and via the transcription factor signal transducer and activator of transcription-3 to activate various types of neurone. Obese rodents, and possibly man, are resistant to leptin; in some cases because of genetic or perinatal programming (primary resistance), but commonly in response to high leptin levels (secondary resistance). Secondary leptin resistance may be a result of reduced transport of leptin to the brain or down-regulation of leptin signalling. Signals that reflect lipid stores form the tonic homeostatic regulatory system. They interact with episodic homeostatic signals carried by neurones, hormones and metabolites to regulate meal size and frequency. They also interact with signals related to the palatability of food, biorhythms and learning. Many neurotransmitters and hormones mediate responses to more than one input (e.g. gastric and adipocyte leptin), but are nevertheless most involved with particular inputs (e.g. leptin with adipocyte fat stores). Feeding can be divided into appetitive (preparation for feeding) and consummatory phases, which can both be further subdivided. Different sets of neurotransmitters and hormones are involved at each stage. In the long term it may be possible to customise obesity therapies according to those inputs and outputs that are most disturbed and most amenable to intervention in individual subjects.

Energy balance mechanisms: Leptin resistance: Orexin

The regulation of energy balance is complex and in man imprecise. Moreover, it is obvious to populations living in societies where food is plentiful and the need for activity limited that regulation works better in preventing death from anorexia than in preventing obesity. It has even been suggested that regulation of energy balance in man is entirely achieved by conscious effort, but this suggestion is difficult to reconcile with the fact that a consistent 10 % (e.g. 1043 kJ (250 kcal) per d) error in energy balance would lead to the accumulation, or loss, of 13 kg adipose tissue in 1 year. Can even this level of control over weight really be exerted by conscious effort? Failure would lead to gross obesity, or death, within a few years. It is not supposed that other animals regulate their weight by conscious effect, nor is it suggested that human subjects regulate their water balance by such means. Energy balance must be regulated, albeit with varying accuracy, in man as in other species including, of course, the laboratory rat and mouse, from which so much has been learned. It is only necessary to look to those animals

Abbreviations: AMPK, AMP-activated protein kinase; GLP, glucagon-like peptide; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; SOCS-3, suppressor of cytokine signalling-3.

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(*ob*/*ob* mice) and individuals lacking functional leptin (Montague *et al*. 1997) to see a mechanism that can go horribly wrong.

In the present article, beginning with leptin, an attempt will be made to illustrate how energy balance is regulated by a variety of inputs, which in turn influence energy expenditure and intake in various ways.

Tonic indicators of fat stores: leptin and insulin

For energy balance to be regulated accurately in the long term there must be a signal or signals that reflect the size of the energy stores. For the situation to be otherwise would be like attempting to regulate the temperature of a building using information about its insulation and the external temperature without having a thermostat that measures the actual temperature inside the building. This approach would be doomed to failure. The focus will be on fat stores; to cover the regulation of carbohydrate stores and protein is less relevant to obesity and would require a much longer article.

The cytokine hormone leptin is released from adipocytes, especially fat-filled adipocytes. Leptin does not only affect energy balance and it does not only act in the brain, but for the purposes of the present article the key point is that it acts via receptors in the hypothalamus to reduce energy intake. Moreover, it increases energy expenditure, primarily by increasing the activity of the sympathetic nervous system (Seals & Bell, 2004), although the impact of this effect on energy balance may be greater in rodents than in man.

Leptin may not be the only signal that indicates the size of lipid stores to the hypothalamus. Long before leptin was discovered in 1994 it had been argued that insulin provides such a signal (see Woods & Seeley, 2001). Insulin is not released from adipocytes, but obesity is associated with peripheral insulin resistance. Consequently, the blood glucose concentration, both before and after a meal, tends to be elevated in obesity, stimulating insulin release from the islets of Langerhans. Like leptin, insulin affects energy expenditure as well as intake, at least in rodents.

An obvious problem with the idea that insulin promotes a negative energy balance is that when given peripherally insulin and insulin secretagogues have the opposite effect of promoting weight gain. However, this anabolic response appears to be entirely mediated by peripheral insulin receptors. Central (third ventricle) administration of insulin reduces energy intake, whilst administration of an insulin antibody into the ventromedial hypothalamus increases intake. There are insulin receptors in the hypothalamus, and administration of antisense mRNA to these receptors also increases food intake (Obici *et al*. 2002). Similarly, selective knock out of the insulin receptor in the brain of mice results in an obese phenotype, whereas knock out of protein tyrosine phosphatase 1B, which deactivates the insulin receptor and insulin receptor substrates (and also the leptin receptor), results in resistance to obesity. The brain and cerebrospinal fluid contain insulin, but since the brain produces little or no insulin, it must come from the periphery, consistent with there being both high plasma and cerebrospinal fluid insulin in obese subjects (for review, see Woods & Seeley, 2001). Finally, a small-molecular-weight insulin receptor agonist has been shown to reduce food intake and increase expenditure when given either centrally or peripherally, possibly because it penetrates the brain better than insulin (Air *et al*. 2002).

Central resistance to leptin and insulin

Most obese individuals have an elevated plasma leptin level. Analogy with elevated insulin levels in mild to moderate type 2 diabetes related to insulin resistance has led to the idea that obese individuals are ‘leptin resistant’. It has not, however, been shown that obese and lean individuals respond differently to similar levels of leptin in the way that subjects with diabetes show reduced glucose disposal during the euglycaemic hyperinsulinaemic clamp. Also, it cannot be shown that the isolated hypothalami of obese individuals respond poorly to leptin in the way that studies can be conducted on isolated adipose or muscle tissue from subjects with diabetes. Leptin levels might simply be raised in response to adiposity, just as insulin is raised in response to high blood glucose after a meal (Arch *et al*. 1998). It is difficult to distinguish cause and effect in the case of obesity and leptin; subjects with diabetes can be studied in the fasted state, whereas the stimulus (adiposity) to leptin secretion in obese subjects is always present. Leptin is clearly not entirely without effect in obese subjects or they would show the rampant obesity of those rare subjects who lack leptin.

Nevertheless, it is unlikely that rodent obesity reveals nothing about human obesity, and it is a common finding that food intake in obese rodents, with the notable exception of *ob*/*ob* mice, responds poorly to exogenous leptin, especially when leptin is injected peripherally. In some models (e.g. *db*/*db* mice) this poor response is because the leptin receptor gene is mutated (very rare in man), and in others (e.g. yellow obese A^y mice) a mutation in one of the downstream pathways may contribute to resistance. However, leptin resistance is also found in diet-induced obesity, where the genomes of the obese and lean animals are identical.

One possible explanation for leptin resistance in diet-induced obesity is that leptin is relatively ineffective in countering hedonistic feeding. Thus, sensitivity to leptin returns very quickly when still-obese animals are returned to a chow diet (Widdowson *et al*. 1997*a*,*b*; Lin *et al*. 2001). Another possibility is that in obesity endogenous leptin levels produce an approximately maximal response, so that exogenous leptin can have little further effect.

Most emphasis, however, has been given to evidence that the penetration of leptin through the blood – brain barrier is reduced in obesity; or that leptin signalling is reduced. Of these hypotheses, the former is supported by evidence that intracerebroventricularly-injected leptin can reduce food intake in obese animals when intraperitoneal leptin is ineffective (Halaas *et al*. 1997; Van Heek *et al*. 1997); also, that penetration of leptin into the brain is reduced in dietary obesity (Banks & Farrell, 2003). On the other hand, poor transport of leptin into the brain cannot easily explain why resistance can occur to the anorexic action but not the sympatho-excitatory action of leptin

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(Mark *et al*. 2002), nor can it explain why old rats are insensitive to both peripherally- and centrally-administered leptin (Scarpace & Tumer, 2001). Low-molecular-weight leptin mimetics that do not enter the brain by the same mechanism as leptin have been reported (Maneuf *et al*. 2004; PJ Richardson, personal communication). At least one of these compounds appears to be more effective in dietary obesity than leptin, suggesting that the blood–brain barrier restricts access of leptin to parts of the brain that regulate feeding, if not sympathetic activity.

If penetration of leptin into the brain is not the whole problem, then reduced leptin signalling might result from an elevated level of suppressor of cytokine signalling-3 (SOCS-3). SOCS-3 is produced in response to activation of the leptin receptor (long form) and feeds back to inhibit further signalling via the transcription factor signal transducer and activator of transcription-3 (El-Haschimi *et al*. 2000). Although SOCS-3 probably plays a role, this theory fails to explain why ciliary neurotrophic factor is far more effective than leptin in preventing diet-induced obesity (Gloaguen *et al*. 1997), despite inducing SOCS-3 expression (Kelly *et al*. 2004). It also fails to explain why leptin is able to activate signal transducer and activator of transcription-3 when leptin resistance is induced by administration of leptin itself (Scarpace *et al*. 2003).

Irrespective of whether SOCS-3 is involved, leptin may fail to activate downstream neurones (see p. 42) such as those expressing pro-opiomelanocortin (POMC) neurones, or to inhibit neuropeptide Y (NPY) neurones (Scarpace *et al*. 2003), although other evidence indicates that hypothalamic NPY neurones remain responsive to elevated leptin levels in obesity (Mantzoros *et al*. 1998; Hansen *et al*. 2004). A recent report suggests that resistance to the anorectic effect of an α-melanocyte-stimulating hormone mimetic is a result of compensatory up-regulation of NPY and agouti-related protein mRNA (Bluher *et al*. 2004), illustrating how resistance may occur downstream of SOCS-3.

Thus, the combination of obesity and high circulating leptin levels in man could have a variety of causes (Fig. 1). First, the association of obesity and high leptin levels could simply reflect the fact that obesity is a consequence of an environment (amount and type of food available; learning; opportunity for exercise) that leptin does not influence or adequately oppose. This state does not deserve to be described as 'leptin resistance'. Second, there could be a permanent deficiency in the response to leptin programmed by genetics and/or life (especially perinatal) experience (Levin, 2000). It is proposed that this state should be termed 'primary leptin resistance'. Third, leptin resistance, like resistance to many other hormones and neurotransmitters, may be a response to high leptin levels; i.e. 'secondary leptin resistance'.

There is clear evidence that secondary leptin resistance occurs. For example, it is produced by intracerebroventricular injection of recombinant adeno-associated virus encoding leptin cDNA into rats (Scarpace *et al*. 2003). Conversely, the obese lethal yellow (A^y/a) mouse, which has a high plasma leptin level, resists the suppressive effect of leptin on food intake, whereas the combined *ob*/*ob*/A^y/a mouse, which has no plasma leptin, is even more obese but is sensitive to leptin (Boston *et al*. 1997).

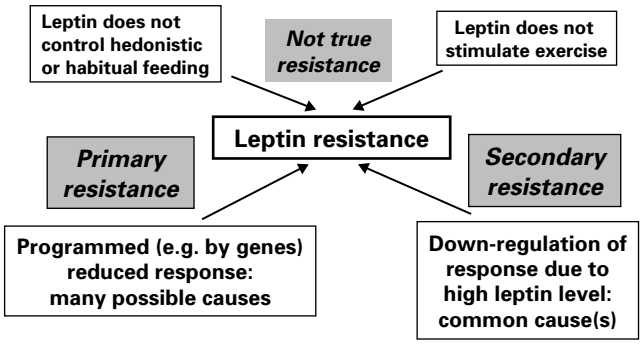

Fig. 1. Causes of leptin resistance: a top-level view.

Just as leptin resistance might cause or exacerbate obesity, so might central insulin resistance. Again, multiple mechanisms might be involved. There appears to be reduced transport of insulin into the brain of obese dogs (Kaiyala *et al*. 2000). In addition, there is evidence that both central insulin and central leptin resistance in obese rats may be partly a result of failure to activate phosphatidylinositol 3-kinase (Carvalheira *et al*. 2003; Niswender & Schwartz, 2003).

Transmission of the leptin signal within the hypothalamus

While the leptin system defends body weight, it does not, unless a very broad definition of the 'leptin system' is used, determine what body weight is to be defended. The defended body weight is not a precise set 'point', since it is very susceptible to environmental influences. It is obviously partly hard-wired by numerous genes, as the many GM animals with altered sensitivity to obesity reveal (Arch, 2002). However, the defended body weight can also change during adult life, which has been clearly shown in Siberian hamsters (*Phodopus sungorus*) changed from long to short daylight periods to mimic the approach of winter. As 'winter' approaches body weight (surprisingly) falls and sensitivity to leptin (associated with decreased SOCS-3 gene expression) increases (Tups *et al*. 2004). Permanent alteration of the defended body weight may also occur following dietary intervention (Levin, 2000), and perhaps is responsible for 'middle-age spread' (Gabriely *et al*. 2002).

Returning to leptin, this cytokine hormone binds to one long form and several short forms of its receptor, produced by mRNA splicing. The long form seems to be essential for the regulation of energy balance because it is this form that is absent in *db/db* mice. Unlike the short forms, the long form can activate signal transducer and activator of transcription-3. Nevertheless, activation of phosphatidylinositol 3-kinase, which requires only the short form of the receptor, also appears to be essential for leptin to inhibit feeding and activate the sympathetic nervous systems. Moreover, phosphatidylinositol 3-kinase also mediates the feeding response to insulin (Niswender & Schwartz, 2003; Rahmouni *et al*. 2003).

The long form of the leptin receptor is expressed in the arcuate, lateral, dorsomedial and ventromedial areas of the hypothalamus (Heritier *et al*. 1997; Elmquist *et al*. 1998).

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In the arcuate nucleus it suppresses the activity of neurones that contain the orexigenic peptides NPY and agouti-related protein, and stimulates activity of neurones that release anorexigenic peptides, notably α-melanocyte-stimulating hormone, derived from POMC, and cocaine- and amphetamine-related transcript. The involvement of two types of neurone and four peptides may amplify responses to leptin (agouti-related protein actually blocks the activation of melanocortin-3 and -4 receptors by α-melanocyte-stimulating hormone), but NPY/agouti-related protein and POMC/cocaine- and amphetamine-regulated transcript neurones also appear to have somewhat different roles. Thus, in one study the hypothalamic prepro-NPY mRNA level has been found to vary across a wider range of leptin concentrations than the POMC mRNA level (Ahima *et al*. 1999); in another study inhibition of fatty acid oxidation has been reported to alter NPY expression but not POMC expression (Obici *et al*. 2003). POMC and NPY neurones then activate different signalling systems. Mutation of Tyr1138 on the long form of the leptin receptor, so that it can still activate phosphatidylinositol 3-kinase but not signal transducer and activator of transcription-3, blocks leptin signalling via POMC, whereas NPY signalling is nearly normal. The phenotype of these mice when compared with that of *db/db* mice, in which both NPY and POMC signalling are blocked, indicates that NPY, but not POMC, mediates growth and gonadal responses to leptin (Bates & Myers, 2003). This deduction is supported by the absence of any effect of stimulation or inhibition of α-melanocyte-stimulating hormone (melanocortin) receptors on the reproductive–endocrine axis (Hohmann *et al*. 2000).

The lateral hypothalamus also contains neurones that express one, but not both, of the orexigenic peptides melanin-concentrating hormone or orexin-A. (Orexin-B is derived from the same propeptide as orexin-A, but has less effect on feeding; some studies have found no effect.) While leptin receptors are present on a proportion of both melanin-concentrating hormone and orexin neurones, only melanin-concentrating hormone plays an important role in the transmission of the leptin signal. Thus, hypothalamic expression of prepro-melanin-concentrating hormone mRNA is increased in situations (e.g. fasting, *ob/ob* mice) in which leptin signalling is low and suppressed by administration of leptin (Griffond & Baker, 2002). By contrast, hypothalamic expression of prepro-orexin mRNA is not elevated in animals with a defective leptin system, and there are conflicting reports as to how fasting or administration of leptin affects prepro-orexin mRNA expression (Smart *et al*. 2002).

So far the discussion has been primarily about the regulation of energy balance by the tonic homeostatic system, i.e. that system in which leptin and possibly insulin play key roles. The main involvement of orexin-A seems to be in the episodic homeostatic regulatory system.

Episodic homeostatic regulation of feeding

Feeding is not a continuous activity; it is episodic. There must, therefore, be episodic signals that regulate the initiation, termination and suppression of feeding (i.e. meals), and these episodic signals must interact with the tonic signals already discussed in order to regulate total energy intake. Episodic signals that indicate nutrient availability are derived from the gut, liver and blood. In addition, there are episodic signals that relay information about circadian, seasonal and reproductive rhythms, stress and other factors (Berthoud, 2002; Strubbe & Woods, 2004), which are beyond the scope of the present article.

Orexin-A and fuel sensing

First, to return to orexin-A, what is the evidence that it plays a role in the episodic homeostatic regulation of feeding? The evidence concerns glucose sensing. 'Glucose sensitive' (also know as 'glucose-inhibited') neurones are active when brain glucose levels are low. One of the areas where they are found is the lateral hypothalamus (Levin, 2002), which is where orexin cell bodies are found. It is well established that glucose-sensitive neurones mediate feeding responses to hypoglycaemia, but it is also possible that small dips in blood glucose before meals play a role in the initiation of feeding. Thus, glucosensing neurones (a term that includes neurones activated and inhibited by glucose) respond to physiological changes in glucose concentration (Routh, 2002).

Various workers have shown that hypoglycaemia causes an increase in hypothalamic prepro-orexin mRNA and increased expression of cFos in orexin neurones (Cai *et al*. 2002; Smart *et al*. 2002). It does not appear that orexin neurones sense glucose directly, but rather that they form synapses with other glucosensing neurones in the lateral hypothalamus and receive inputs from such neurones in the nucleus of the solitary tract (Cai *et al*. 2002).

Some workers dismiss the role of orexin-A in the normal regulation of feeding, arguing that it stimulates feeding only because it promotes arousal. However, orexin-B promotes arousal more effectively than orexin-A and has less effect on feeding. Moreover, neuropeptide E-I (derived from prepro-melanin-concentrating hormone) potently stimulates grooming, rearing and locomotor activity, but has no effect on feeding. Arousal may be involved in the orexigenic effect of orexin-A, but probably orexin-B and the orexin-2 receptor have more effect on arousal, whereas feeding is stimulated by activation of the orexin-1 receptor. Indeed, an orexin-1 receptor antagonist has been reported to show anti-obesity activity in *ob/ob* mice (Haynes *et al*. 2002) but does not disrupt normal behaviour (Rodgers *et al*. 2001).

Blood lipids as well as glucose may influence feeding, and some glucosensing neurones may be better described as fuel-sensing neurones (Levin, 2002). Thus, central administration of oleic acid inhibits food intake in rats. The metabolites that link fatty acids to the activity of neurones that regulate feeding are unclear. Fatty acyl-CoA, malonyl-CoA and products of fatty acid or glucose oxidation have all been implicated (Hu *et al*. 2003; Obici & Rossetti, 2003; Wortman *et al*. 2003).

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Gut signals

Whilst blood metabolites signal directly to the brain, there are also a number of signals from the gut and pancreas that indicate that nutrients are entering, or will soon enter, the blood. In addition to gastric distension, these signals include the hormones cholecystokinin, gastrin-releasing peptide, amylin, enterostatin, glucagon-like peptide (GLP)-1 and -2, ghrelin, peptide $YY_{3–36}$, pancreatic polypeptide and oxyntomodulin (Blevins *et al*. 2002; Konturek *et al*. 2004; Stanley *et al*. 2004). Why so many? Of course, they have other varied roles, such as potentiation of glucose-stimulated insulin secretion (GLP-1), or alteration of the motility of various parts of the gastrointestinal tract, but why do they all affect feeding as well? First, ghrelin differs from the other gut peptides in that it stimulates feeding and appears to be involved in the initiation of feeding. Second, the process of satiation and the period of satiety that follows must involve a cascade of signals (Blundell *et al*. 2001). By having signals released from various parts of the gut, a system able to predict the entry of nutrients into the circulation is possible: ghrelin is produced by the stomach; amylin, enterostatin and pancreatic polypeptide are produced by the pancreas; cholecystokinin is most concentrated in the duodenum and jejunum; oxyntomodulin is released from the distal ileum; GLP-1 is produced mainly in the ileum and colon (although GLP-1 levels rise rapidly after a meal); peptide YY is most highly concentrated in the distal ileum, colon and, particularly, the rectum.

Third, different peptides may be released by different nutrients. The mechanisms that enable animals to eat a balance of macronutrients and sometimes select foods that contain needed micronutrients remain largely a mystery (Thibault & Booth, 1999). The pentapeptide enterostatin, derived from pancreatic procolipase, selectively inhibits fat intake (Erlanson-Albertsson & York, 1997). Cholecystokinin may also selectively respond to and inhibit fat intake (Burton-Freeman *et al*. 1999) and the effect of enterostatin on fat intake is dependent on cholecystokinin-A receptors (Lin *et al*. 2003). By contrast with enterostatin and cholecystokinin, GLP-1 and oxyntomodulin, which are derived from the same proglucagon gene, respond well to carbohydrate.

Central mediators of episodic signalling

The gut peptides may be transported in the blood and signal to the brain directly, but they also act via vagal afferents and the nucleus of the solitary tract in the caudal brain stem, which communicates with the hypothalamus. Within the central nervous system serotonin has been implicated in within-meal satiation and post-meal satiety; it may be less involved in the leptin-mediated tonic regulation of energy balance (Halford & Blundell, 2000). There is also evidence that it plays a role in satiety in response to fat (Burton-Freeman *et al*. 1999; Halford & Blundell, 2000).

Galanin is another neurotransmitter that has been proposed to regulate fat intake. It acts primarily in the paraventricular nucleus and, in contrast to serotonin, is orexigenic. The evidence that it selectively promotes fat intake is, however, controversial (Crawley, 1999).

Hedonic regulation of feeding

If animals are to eat, they must experience some reward; if they are to select foods with a variety of nutrients, they must be rewarded by their selections. The systems that regulate reward are usually classified as ‘hedonic’ and are excluded from the homeostatic systems, presumably because unchecked hedonism can lead to obesity. Nevertheless, the hedonic system interacts with the homeostatic system. For example, leptin suppresses the responses of taste cells to sweet substances (Kawai *et al*. 2000).

A number of neurotransmitters have been implicated in the hedonic regulation of feeding; opioid agonists, γ-aminobutyric acid agonists, glutamate antagonists and cannabinoids all preferentially increase consumption of palatable foods (Saper *et al*. 2002), whilst the cannabinoid receptor-1 receptor antagonist rimonabant, which is in phase III anti-obesity trials for obesity, selectively reduces intake of a sucrose solution in rats (Harrold & Williams, 2003). The nucleus accumbens, hippocampus and amygdala are some sites where these agents act to affect reward.

Multiple roles for signalling systems

Thus far, the impression may have been given that the various signals play specific roles in the tonic or episodic homeostatic systems, or in the hedonic regulation of feeding. This position is far from the truth.

Leptin, for example, is not only released from fat-filled adipocytes, it is also released from the stomach in response to feeding and is proposed to play a role in the episodic regulation of feeding (Pico *et al*. 2003). Orexins are found in gut neurones that respond to feeding (Kirchgessner & Liu, 1999). Some gut peptides are also expressed in the central nervous system; a well-documented case is GLP-1, which appears to act in the paraventricular nucleus of the hypothalamus and in the central nucleus of the amygdala (Gunn *et al*. 1997). Peptide YY and pancreatic polypeptide, acting via NPY Y_2 and Y_4 receptors respectively, actually have opposing effects on appetite depending on whether they are given peripherally or centrally (Wynne *et al*. 2004). Serotonin released by fenfluramine activates central melanocortin pathways (Heisler *et al*. 2002), suggesting an involvement in tonic regulatory mechanisms, as well as the episodic regulatory role described earlier. Cannabinoids appear not only to act outside the hypothalamus to influence hedonic feeding but, within the hypothalamus, where they are suppressed by leptin (Harrold & Williams, 2003).

Two recent papers (Andersson *et al*. 2004; Minokoshi *et al*. 2004) suggest that a common signal for many systems that regulate energy balance is the enzyme AMP-activated protein kinase (AMPK). Thus, leptin, a synthetic melanocortin receptor-3/4 agonist and glucose (all anorexigenic) reduce the activity of AMPK in the whole hypothalamus or various hypothalamic nuclei, whereas ghrelin and agouti-related protein increase AMPK activity. Activation of AMPK with an AMP analogue stimulates feeding. Dominant negative expression of AMPK reduces food intake, while constitutively-active expression

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increases food intake and markedly attenuates the anorexigenic effect of leptin. AMPK is proposed to play a role in NPY neurones but not POMC neurones in the arcuate nucleus, and also in downstream neurones in the paraventricular nucleus (Minokoshi *et al*. 2004).

Selective activation of outputs

It has already been explained that some gut peptides and central neurotransmitters play roles in the selection of macronutrients and palatable foods, and also that resistance to the action of leptin can be selective for food intake rather than energy expenditure. However, the outputs that regulate energy balance can be dissected into far more components.

Feeding is broadly divided into appetitive behaviour (alertness, locomotor activity, killing and, especially in man, preparation of food) and consummatory behaviour (the more stereotypic process of eating; Robbins & Everitt, 1996). NPY (orexigenic) stimulates appetitive responses used to obtain food, but it actually inhibits responses involved in consuming food when it is in the mouth. Leptin (anorexigenic) has the opposite effects; it directs attention away from food (Ammar *et al*. 2000). Another way of investigating feeding is to make rats press levers to obtain food. The cannabinoid antagonist rimonabant reduces the motivation to feed in this scenario. Since it reduces the motivation to feed before the rats have eaten, it cannot be argued that it is reducing palatability or reward (Thornton-Jones *et al*. 2004).

The consummatory phase of feeding can be analysed in terms of meal size, meal frequency and rate of eating. Leptin selectively reduces meal size (Eckel *et al*. 1998; Hulsey *et al*. 1998; Kahler *et al*. 1998). Fenfluramine, acting via elevation of serotonin concentration in the synapse, reduces both meal size and feeding rate, but the precise role of 5-hydroxytryptamine$_{1B}$ and 5-hydroxytryptamine$_{2C}$ receptors in mediating these responses remains unclear (Clifton, 2000; Clifton *et al*. 2000). Dopamine, via the D2 receptor, reduces meal size but increases meal frequency. It has been suggested that it enhances the rate of switching from feeding to other behaviours (Clifton, 2000).

Thermogenic mechanisms may also be activated selectively (Morrison, 2001), but there is no evidence that leptin can selectively activate the sympathetic nervous system to stimulate thermogenesis but not the cardiovascular system (Hausberg *et al*. 2002).

Mammals have developed a long way compared with a sea-slug that has one hormone for eating and another for sex (Williams & Bloom, 1987). Body weight is regulated by numerous tonic, episodic and hedonic stimuli. These stimuli signal in numerous ways to the central nervous system, which integrates the inputs relative to its 'harder wiring' and regulates both the many components of feeding behaviour and various outputs that affect energy expenditure. The epidemic of obesity is not a result of any new failure of the tonic system, it has simply been overwhelmed by the changing environment. To combat obesity either the environment (personal or general) must be altered, or drugs must be sought that block episodic or hedonic influences, or make the tonic regulation of body weight more effective. Understanding individual disturbances of inputs and outputs may, in the long term, allow the customisation of the treatment of obesity, whether achieved by diet or other behavioural interventions, or by pharmacotherapy.

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