STARLING REVIEW

Appetite control

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Abstract

Our understanding of the physiological systems that regulate food intake and body weight has increased immensely over the past decade. Brain centres, including the hypothalamus, brainstem and reward centres, signal via neuropeptides which regulate energy homeostasis. Insulin and hormones synthesized by adipose tissue reflect the long-term nutritional status of the body and are able to influence these circuits. Circulating gut hormones modu-

late these pathways acutely and result in appetite stimulation or satiety effects. This review discusses central neuronal networks and peripheral signals which contribute energy homeostasis, and how a loss of the homeostatic process may result in obesity. It also considers future therapeutic targets for the treatment of obesity.

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Introduction

In most adults, adiposity and body weight are remarkably constant despite huge variations in daily food intake and energy expended. A powerful and complex physiological system exists to balance energy intake and expenditure, composed of both afferent signals and efferent effectors. This system consists of multiple pathways which incorporate significant redundancy in order to maintain the drive to eat. In the circulation, there are both hormones which act acutely to initiate or terminate a meal and hormones which reflect body adiposity and energy balance. These signals are integrated by peripheral nerves and brain centres, such as the hypothalamus and brain stem. The integrated signals regulate central neuropeptides, which modulate feeding and energy expenditure. This energy homeostasis, in most cases, regulates body weight tightly. However, it has been argued that evolutionary pressure has resulted in a drive to eat without limit when food is readily available. The disparity between the environment in which these systems evolved and the current availability of food may contribute to over-eating and the increasing prevalence of obesity.

Current concepts

Hypothalamic neuropeptides

In order to maintain a stable body weight over a long period of time, we must continually balance food intake

with energy expenditure. The hypothalamus was first implicated in this homeostatic process over 50 years ago. Lesioning and stimulation of the hypothalamic nuclei initially suggested roles for the ventromedial nucleus as a 'satiety centre' and the lateral hypothalamic nucleus (LHA) as a 'hunger centre' (Stellar 1994). However, rather than specific hypothalamic nuclei controlling energy homeostasis, it is now thought to be regulated by neuronal circuits, which signal using specific neuropeptides. The arcuate nucleus (ARC), in particular, is thought to play a pivotal role in the integration of signals regulating appetite.

The ARC is accessible to circulating signals of energy balance, via the underlying median eminence, as this region of the brain is not protected by the blood–brain barrier (Broadwell & Brightman 1976). Some peripheral gut hormones, such as peptide YY and glucagon-like peptide 1, are able to cross the blood–brain barrier via non-saturable mechanisms (Nonaka *et al.* 2003, Kastin *et al.* 2002). However, other signals, such as leptin and insulin, are transported from blood to brain by a saturable mechanism (Banks *et al.* 1996, Banks 2004). Thus, the blood–brain barrier has a dynamic regulatory role in the passage of some circulating energy signals.

There are two primary populations of neurons within the ARC which integrate signals of nutritional status, and influence energy homeostasis (Cone *et al.* 2001). One neuronal circuit inhibits food intake, via the expression of the neuropeptides pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) (Elias *et al.* 1998a, Kristensen *et al.* 1998). The other

Figure 1 The ARC and the control of appetite. α -MSH, α -melanocyte-stimulating hormone; GHS-R, growth hormone secretagogue receptor.

neuronal circuit stimulates food intake, via the expression of neuropeptide Y (NPY) and agouti-related peptide (AgRP) (Broberger *et al.* 1998a, Hahn *et al.* 1998). See Figure 1.

NPY NPY is one of the most abundant neurotransmitters in the brain (Allen *et al.* 1983). Hypothalamic levels of NPY reflect the body's nutritional status, an essential feature of any long-term regulator of energy homeostasis. The levels of hypothalamic NPY mRNA and NPY release increase with fasting and decrease after refeeding (Sanacora *et al.* 1990, Kalra *et al.* 1991, Swart *et al.* 2002). The ARC is the major hypothalamic site of NPY expression (Morris 1989). ARC NPY neurons project to the ipsilateral paraventricular nucleus (PVN) (Bai *et al.* 1985), and repeated intracerebroventricular (icv) injection of NPY into the PVN causes hyperphagia and obesity (Stanley *et al.* 1986, Zarjevski *et al.* 1993). Central administration of NPY also reduces energy expenditure, resulting in reduced brown fat thermogenesis (Billington *et al.* 1991), suppression of sympathetic nerve activity (Egawa *et al.* 1991) and inhibition of the thyroid axis (Fekete *et al.* 2002). It also results in an increase in basal plasma insulin level (Moltz & McDonald 1985, Zarjevski *et al.* 1993) and morning cortisol level (Zarjevski *et al.* 1993), independent of increased food intake.

Although NPY seems to be an important orexigenic signal, NPY-null mice have normal body weight and adiposity (Thorsell & Heilig 2002), although they demonstrate a reduction in fast-induced feeding (Bannon *et al.* 2000). This absence of an obese phenotype may be due to the presence of compensatory mechanisms or alternative orexigenic pathways, such as those which signal via AgRP (Marsh *et al.* 1999). It is possible that there is evolutionary redundancy in orexigenic signalling in order to avert starvation. This redundancy may also contribute to the difficulty elucidating the receptor subtype that mediates NPY-induced feeding (Raposo *et al.* 2004).

NPY is part of the pancreatic polypeptide (PP)-fold family of peptides, including peptide YY (PYY) and pancreatic polypeptide (PP). This family bind to seven-transmembrane-domain G-protein-coupled receptors, designated Y_1 – Y_6 (Larhammar 1996). Y_1 – Y_5 receptors have been demonstrated in rat brain, but Y_6 , identified in mice, is absent in rats and inactive in primates (Inui 1999). The Y_1 , Y_2 , Y_4 and Y_5 receptors, cloned in the hypothalamus, have all been postulated to mediate the orexigenic effects of NPY. The feeding effect of NPY may indeed be mediated by a combination of receptors rather than a single one.

Administration of antisense oligonucleotides to the Y_5 receptor inhibits food intake (Schaffhauser *et al.* 1997), and

Y_5 receptor-deficient mice have an attenuated response to NPY (Marsh *et al.* 1998). However, Y_5 receptor density in the hypothalamus appears to be reduced in response to fasting and upregulated in dietary-induced obesity (Widdowson *et al.* 1997). In addition, antagonists to the Y_5 receptor have no major feeding effects in rats (Turnbull *et al.* 2002), and Y_5 receptor-deficient mice develop late-onset obesity, rather than the expected reduction in body weight (Marsh *et al.* 1998). It has been postulated that the Y_5 receptor may maintain the feeding response rather than initiate feeding in response to NPY, as Y_5 receptor antisense oligonucleotide decreases food intake 10 h after NPY- or PP-induced feeding, but has no effect on the initial orexigenic response (Flynn *et al.* 1999).

NPY-induced and fast-induced feeding is prevented by antagonists to the Y_1 receptor (Kanatani *et al.* 1996, Wieland *et al.* 1998), and is reduced in Y_1 receptor-knockout mice (Kanatani *et al.* 2000). However, like Y_5 receptors, ARC Y_1 receptor numbers, distribution and mRNA, are reduced during fasting, an effect which is attenuated by administration of glucose (Cheng *et al.* 1998). Furthermore, NPY fragments with weak affinity to the Y_1 receptor still elicit a similar dose-dependent increase in food intake to NPY, suggesting that the Y_1 receptor may not be mediating its effect (O'Shea *et al.* 1997). Y_1 receptor-deficient mice are obese, but are not hyperphagic, suggesting that the Y_1 receptor may affect energy expenditure rather than feeding (Kushi *et al.* 1998).

The presynaptic Y_2 and Y_4 receptors have an auto-inhibitory effect on NPY neurons (King *et al.* 1999, 2000). As expected, Y_2 receptor-knockout mice have increased food intake, weight and adiposity (Naveilhan *et al.* 1999). However, Y_2 receptor conditional-knockout mice (perhaps with more normal development of the neuronal circuits) have a temporarily reduced body weight and food intake, which returns to normal after a few weeks (Sainsbury *et al.* 2002). There is also evidence for a role of Y_4 receptors in the orexigenic NPY response. PP has a relative specificity for the Y_4 receptor and central administration has been shown to elicit food intake in both mice (Asakawa *et al.* 1999) and rats (Campbell *et al.* 2003).

The melanocortin system Melanocortins, including adrenocorticotrophin and melanocyte-stimulating hormones (MSHs), are peptide-cleavage products of the POMC molecule and exert their effects by binding to the melanocortin receptor family. Levels of POMC expression reflect the energy status of the organism. POMC mRNA levels are reduced markedly in fasted animals and increased by exogenous administration of leptin, or restored by refeeding after 6 h (Schwartz *et al.* 1997, Swart *et al.* 2002). Mutations within the POMC gene or abnormalities in the processing of the POMC gene product result in early-onset obesity, adrenal insufficiency and red hair pigmentation in humans (Krude *et al.* 1998). The loss of one copy of the POMC gene in mice is sufficient to render

them susceptible to diet-induced obesity (Challis *et al.* 2004).

Melanocortin 3 (MC3R) and melanocortin 4 receptors (MC4R) are found in hypothalamic nuclei implicated in energy homeostasis, such as the ARC, ventromedial nucleus (VMH) and PVN (Mountjoy *et al.* 1994, Harrold *et al.* 1999). Lack of the MC4R leads to hyperphagia and obesity in rodents (Fan *et al.* 1997, Huszar *et al.* 1997) and these receptors are implicated in 1–6% of severe early-onset human obesity (Farooqi *et al.* 2000, Lubrano-Berthelier *et al.* 2003a, 2003b). Polymorphism of this receptor has also been implicated in polygenic late-onset obesity in humans (Argyropoulos *et al.* 2002).

Although the involvement of the MC4R in feeding is established, the function of the MC3R is still unclear. A selective MC3R agonist has been found to have no effect on food intake (Abbott *et al.* 2000), and although the MC4R is influenced by energy status, the MC3R is not (Harrold *et al.* 1999). However, there is some evidence that both the MC3R and MC4R are able to influence energy homeostasis. The MC3R/MC4R antagonist, AgRP, is able to increase food intake in MC4R-deficient mice (Butler 2004). Mice which lack the MC3R, although not overweight on a normal diet, have increased adiposity, and seem to switch from fat to carbohydrate metabolism (Butler *et al.* 2000). However, MC3-null mice are obese and develop increased adipose tissue when fed on high-fat chow. MC3R mutations have been found in human subjects with morbid obesity (Mencarelli *et al.* 2004).

The main endogenous ligand for the MC3R/MC4R is α -melanocyte-stimulating hormone (α -MSH), which is expressed by cells in the lateral part of the ARC (Watson & Akil 1979). i.c.v. administration of agonists to the hypothalamic MC4R suppresses food intake, and the administration of selective antagonists results in hyperphagia (Benoit *et al.* 2000). In addition to its effects on feeding, α -MSH also stimulates the thyroid axis (Kim *et al.* 2000b) and increases energy expenditure, as measured by oxygen consumption (Pierroz *et al.* 2002), sympathetic nerve activity and the temperature of brown adipose tissue (Yasuda *et al.* 2004).

The agouti mouse is hyperphagic and obese, and expresses the agouti protein ectopically, which is normally restricted to the hair follicle. The agouti protein is a competitive antagonist of α -MSH and melanocortin receptors (Lu *et al.* 1994). The antagonist effect on the peripheral MC1R results in a yellow coat, and its effect on the hypothalamic MC4R results in obesity (Lu *et al.* 1994, Fan *et al.* 1997).

Although the agouti protein is not normally expressed in the brain, a partially homologous peptide, AgRP, is expressed in the medial part of the ARC (Shutter *et al.* 1997). AgRP mRNA increases during fasting (Swart *et al.* 2002) and the peptide is a potent selective antagonist at the MC3R and MC4R (Ollmann *et al.* 1997).

AgRP (83–132), the C-terminal fragment, is able to block the reduction in food intake seen with the icv administration of α -MSH and increase nocturnal food intake (Rossi *et al.* 1998).

Transgenic mice with ubiquitous over-expression of AgRP are obese, but with no alteration of coat colour as AgRP is inactive at the MC1R (Ollmann *et al.* 1997). A polymorphism in the AgRP gene in humans is associated with lower body weight and fat mass (Marks *et al.* 2004). Consistent with its role in energy homeostasis, AgRP and AgRP(83–132) administered icv result in hyperphagia which can persist for a week (Hagan *et al.* 2000, Rossi *et al.* 1998). Although NPY mRNA levels are reduced 6 h after refeeding, AgRP levels remain elevated (Swart *et al.* 2002). This prolonged response results in a greater cumulative effect on food intake than NPY, and probably involves more diverse signalling pathways than the melanocortin pathway alone (Hagan *et al.* 2000, 2001, Zheng *et al.* 2002).

Consistent with the role of AgRP as an orexigenic peptide, the reduction of hypothalamic AgRP RNA by RNA interference results in lower body weight, although this may partly be an effect of increased energy expenditure (Makimura *et al.* 2002). Independent of its orexigenic effects, chronic icv administration of AgRP suppresses thyrotropin-releasing hormone, reduces oxygen consumption and decreases the ability of brown adipose tissue to expend energy (Small *et al.* 2001, 2003).

AgRP and NPY are potent orexigenic molecules which are 90% co-localized in ARC neurons (Hahn *et al.* 1998, Broberger *et al.* 1998a). NPY may inhibit the arcuate POMC neuron via ARC NPY Y₁ receptors (Fuxe *et al.* 1997, Roseberry *et al.* 2004). Activation of ARC NPY/AgRP neurons therefore potentially stimulates feeding via activation of PVN NPY receptors, inhibition of the melanocortin system by ARC Y₁ receptors and antagonism of MC3R/MC4R activation by AgRP in the PVN. However, it has been demonstrated that NPY/AgRP-knockout mice have no obvious feeding or body-weight defects. Furthermore, AgRP is absent from hypothalamic nuclei known to be involved in energy homeostasis, such as the VMH (Broberger *et al.* 1998a). This suggests there must be other signalling pathways which are capable of regulating energy homeostasis (Qian *et al.* 2002).

CART CART is co-expressed with α -MSH in the ARC (Elias *et al.* 1998a, Kristensen *et al.* 1998). Neurons expressing CART are also found in the LHA and PVN (Couceyro *et al.* 1997). Food-deprived animals show a pronounced reduction in CART mRNA within the ARC, whereas peripheral administration of leptin to leptin-deficient *ob/ob* mice results in a stimulation of CART mRNA expression (Kristensen *et al.* 1998). An antiserum against CART peptide (1–102) and CART peptide fragment (82–103), injected icv in rats, increases feeding, suggesting that it is part of the physiological

control of energy homeostasis (Kristensen *et al.* 1998, Lambert *et al.* 1998). CART(1–102) and CART(82–103) injected icv into rats inhibit both the normal and NPY-stimulated feeding response, but result in abnormal behavioural responses at high dose (Kristensen *et al.* 1998, Lambert *et al.* 1998). However, administration of CART(55–102) into discrete hypothalamic nuclei such as the ARC and ventromedial nucleus is able to increase food intake (Abbott *et al.* 2001). Thus, there may be more than one population of CART-expressing neurons which have different roles in feeding behaviour. For instance, NPY release could stimulate a population of CART neurons in the ARC which are orexigenic, producing positive orexigenic feedback (Dhillon *et al.* 2002).

Downstream pathways

Hypothalamic nuclei such as the PVN, dorsomedial hypothalamus (DMH), LHA and perifornical area receive NPY/AgRP and POMC/CART neuronal projections from the ARC (Elias *et al.* 1998b, Elmquist *et al.* 1998b, Kalra *et al.* 1999). These areas contain secondary neurons which process information regarding energy homeostasis. A number of signalling molecules which are expressed in these regions have been shown to be physiologically involved in energy homeostasis (see Figure 2).

PVN The PVN integrates NPY, AgRP, melanocortin and other signals via projections it receives from a number of sites in the brain, including the ARC and nucleus of the solitary tract (NTS) (Sawchenko & Swanson 1983). The PVN is highly sensitive to administration of many peptides implicated in feeding, e.g. cholecystokinin (CCK) (Hamamura *et al.* 1991), NPY (Lambert *et al.* 1995), ghrelin (Lawrence *et al.* 2002), orexin-A (Edwards *et al.* 1999, Shirasaka *et al.* 2001), leptin (Van Dijk *et al.* 1996, Elmquist *et al.* 1997) and glucagon-like peptide 1 (GLP-1) (Van Dijk *et al.* 1996). Administration of a melanocortin agonist directly into the PVN results in potent inhibition of food intake (Giraud *et al.* 1998, Kim *et al.* 2000a), and inhibits the orexigenic effect of NPY administration (Wirth *et al.* 2001), whereas, the administration of a melanocortin antagonist to the PVN results in a potent increase in food intake (Giraud *et al.* 1998). Electrophysiological studies in the PVN have shown that neurons expressing NPY/AgRP attenuate inhibitory GABA-ergic signalling, whereas POMC neurons potentiate GABA-ergic signalling (Cowley *et al.* 1999). GABA-ergic signalling also occurs in a subpopulation of ARC NPY neurons which release GABA locally and inhibit POMC neurons.

Neuropeptides involved in appetite regulation in the PVN may also signal via AMP-activated protein kinase (AMPK), a heterodimer consisting of catalytic α -subunits and regulatory β - and γ -subunits. Multiple anorectic factors including leptin, insulin and MT-II (an MC3R/MC4R agonist) suppress α 2 AMPK activity in the ARC and

Figure 2 Schematic of the hypothalamic nuclei (coronal section). BDNF, brain-derived neurotrophic factor; CRH, corticotrophin-releasing hormone; MCH, melanin-concentrating hormone; ME, median eminence; PFA, perifornical area; TRH, thyrotropin-releasing hormone.

PVN, whereas the $\alpha 2$ AMPK activity is stimulated by orexigenic factors such as AgRP (Andersson *et al.* 2004, Minokoshi *et al.* 2004). A pharmacologically induced increase in the level of AMPK in the PVN results in increased food intake (Andersson *et al.* 2004). $\alpha 2$ AMPK activity may be regulated by the MC4R, as peripheral signals of energy status are unable to modulate $\alpha 2$ AMPK activity in MC4R-knockout mice (Minokoshi *et al.* 2004).

The integration of signals within the PVN initiates changes in other neuroendocrine systems. NPY/AgRP and melanocortin projections from the ARC innervate thyrotropin-releasing hormone neurons in the PVN (Legradi & Lechan 1999, Fekete *et al.* 2000). These projections have an inhibitory effect on pro-thyrotropin-releasing hormone gene expression in the PVN (Fekete *et al.* 2002), whereas α -MSH projections have a stimulatory effect and prevent fasting-induced inhibition of thyrotropin-releasing hormone (Fekete *et al.* 2000). NPY projections to the PVN also act on corticotrophin-releasing hormone-expressing neurons influencing energy homeostasis (Sarkar & Lechan 2003).

DMH The DMH has extensive connections with other hypothalamic nuclei, including the ARC, from which it receives AgRP/NPY projections (Kalra *et al.* 1999). Integration of signals may also take place in the DMH, as α -MSH-positive fibres are in close proximity to NPY-expressing cells in the DMH, and melanocortin agonists attenuate DMH NPY expression and suckling-induced hyperphagia in rats (Chen *et al.* 2004b).

LHA/perifornical area Other hypothalamic sites such as the LHA/perifornical area are also involved in second-

order signalling. Indeed, the perifornical area has been found to be more sensitive to NPY-elicited feeding than the PVN (Stanley *et al.* 1993). The LHA/perifornical area contains neurons expressing melanin-concentrating hormone (MCH) (Marsh *et al.* 2002). Fasting increases MCH mRNA, and repeated icv administration of MCH increases food intake (Qu *et al.* 1996) and results in mild obesity in rats (Marsh *et al.* 2002). Conversely, MCH-1 receptor antagonists reduce feeding and result in a sustained reduction in body weight if administered chronically (Borowsky *et al.* 2002). Transgenic mice over-expressing precursor MCH are hyperphagic and develop central obesity (Marsh *et al.* 2002), whereas mice with a disruption of the MCH gene are hypophagic, lean and have increased energy expenditure, despite reduced ARC POMC and circulating leptin (Shimada *et al.* 1998, Marsh *et al.* 2002). Crosses of leptin-deficient *ob/ob* mice with MCH-null mice result in an attenuation in weight gain and adiposity compared with *ob/ob* mice (Segal-Lieberman *et al.* 2003). This perhaps infers that MCH acts downstream of leptin and POMC, and demonstrates that not all orexigenic peptides show redundancy.

Orexin A and B (or hypocretin 1 and 2) are peptide products of prepro-orexin. The peptides are produced in the LHA/perifornical area and zona incerta by neurons distinct from those which produce MCH (De Lecea *et al.* 1998, Sakurai *et al.* 1998). Orexin neurons exert their effects via wide projections throughout the brain, for example to the PVN, ARC, NTS and dorsal motor nucleus of the vagus (De Lecea *et al.* 1998, Peyron *et al.* 1998). The orexin-1 receptor, which is highly expressed in the VMH, has a much greater affinity for orexin A, whereas the orexin-2 receptor, which is highly expressed

in the PVN, has comparable affinity for both orexin A and B (Sakurai *et al.* 1998). The prepro-orexin mRNA level is increased in the fasting state and central administration has been found to result in both orexigenic behaviour and generalized arousal (Sakurai *et al.* 1998, Hagan *et al.* 1999). Central administration of orexin A has a potent effect on feeding (Haynes *et al.* 1999) and vagally mediated gastric acid secretion (Takahashi *et al.* 1999), whereas orexin B does not. However, although icv administration of orexin A results in increased daytime feeding, there is no overall change in 24-h food intake (Haynes *et al.* 1999). Furthermore, chronic administration of orexin A alone does not increase body weight (Yamanaka *et al.* 1999).

Orexin neurons project to areas associated with arousal and attention as well as feeding, and orexin-knockout mice are thought to be a model of human narcolepsy (Chemelli *et al.* 1999). In circumstances of starvation, the orexin neuropeptides may mediate both an arousal response and a feeding response in order to initiate food-seeking behaviour.

Orexin may also play a role as a peripheral hormone involved in energy homeostasis. Orexin neurons, expressing both orexin and leptin receptors, have been identified in the gastrointestinal tract, and appear to be activated during starvation (Kirchgessner & Liu 1999). Orexin is also expressed in the endocrine cells in the gastric mucosa, intestine and pancreas (Kirchgessner & Liu 1999) and peripheral administration increases blood insulin levels (Nowak *et al.* 2000).

NPY, AgRP and α -MSH terminals are abundant in the LHA and are in contact with MCH- and orexin-expressing cells (Broberger *et al.* 1998b, Elias *et al.* 1998b, Horvath *et al.* 1999). Central orexin neurons also express NPY (Campbell *et al.* 2003) and leptin receptors (Horvath *et al.* 1999) and are thus able to integrate adiposity signals. Further integration of peripheral signals is provided by the large number of glucose-sensing neurons in the LHA (Bernardis & Bellinger 1996). Some studies have hypothesized a role for orexin neurons in sensing glucose levels within this region, and these have shown that hypoglycaemia induces c-Fos expression in orexin neurons (Moriguchi *et al.* 1999) and increases orexin mRNA levels (Cai *et al.* 1999). Glucose signalling also occurs in other hypothalamic nuclei such as the VMH (Dunn-Meynell *et al.* 1997) and in the ARC, where glucose-sensing neurons express NPY (Muroya *et al.* 1999). The mechanism by which the MCH and orexin neurons exert their effects on energy homeostasis has not been fully elucidated. However, it is clear that major targets are the endocrine and autonomic nervous system, the cranial nerve motor nuclei and cortical structures (Saper *et al.* 2002).

VMH The VMH has long been known to play a role in energy homeostasis. Bilateral VMH lesions produce hyperphagia and obesity. The VMH receives projections

from arcuate NPY-, AgRP- and POMC-immunoreactive neurons and in turn VMH neurons project to other hypothalamic nuclei (e.g. DMH) and to brain stem regions such as the NTS. NPY expression is altered in the VMH of obese mice (Guan *et al.* 1998) and MC4R expression is upregulated in the VMH of diet-induced obese rats (Huang *et al.* 2003). Recent work has demonstrated that brain-derived neurotrophic factor (BDNF) is highly expressed within the VMH, where its expression is reduced markedly by food deprivation (Xu *et al.* 2003), and also regulated by melanocortin agonists. Mice with reduced BDNF receptor expression or reduced BDNF signalling have significantly increased food intake and body weight (Rios *et al.* 2001, Xu *et al.* 2003). Thus, VMH BDNF neurons may form another downstream pathway through which the melanocortin system regulates appetite and body weight.

The brainstem pathways

There are extensive reciprocal connections between the hypothalamus and brainstem, particularly the NTS (Ricardo & Koh 1978, van der Kooy *et al.* 1984, Ter Horst *et al.* 1989). In addition to interacting with hypothalamic circuits, the brainstem also plays a principal role in the regulation of energy homeostasis. Like the ARC, the NTS is in close anatomical proximity to a circumventricular organ with an incomplete blood-brain barrier – the area postrema (Ellacott & Cone 2004) – and is therefore in an ideal position to respond to peripheral circulating signals, in addition to receiving vagal afferents from the gastrointestinal tract (Kalia & Sullivan 1982, Sawchenko 1983).

The NTS has a high density of NPY-binding sites (Harfstrand *et al.* 1986), including Y₁ receptors (Glass *et al.* 2002) and Y₅ receptors (Dumont *et al.* 1998). Extracellular NPY levels within the NTS fluctuate with feeding (Yoshihara *et al.* 1996), and NPY neurons from this region project forward to the PVN (Sawchenko *et al.* 1985).

There is also evidence for a melanocortin system in the NTS, separate from that of the ARC (Kawai *et al.* 1984). POMC-derived peptides are synthesized in the NTS of the rat (Kawai *et al.* 1984, Bronstein *et al.* 1992, Fodor *et al.* 1996), and caudal medulla in humans (Grauerholz *et al.* 1998), and these POMC neurons are activated by feeding and by peripheral CCK administration (Fan *et al.* 1997). The MC4R is present in the NTS (Mountjoy *et al.* 1994). Food intake is reduced by the administration of a MC3R/MC4R agonist to the fourth ventricle or dorsal motor nucleus of the vagus nerve, whereas MC3R/MC4R antagonists increase intake (Williams *et al.* 2000).

The reward pathways

The rewarding nature of food may act as a stimulus to feeding, even in the absence of an energy deficit.

The sensation of reward is, however, influenced by energy status, as the subjective palatability of food is altered in the fed, compared with the fasting, states (Berridge 1991). Thus, signals of energy status, such as leptin, are able to influence the reward pathways (Fulton *et al.* 2000).

The reward circuitry is complex and involves interactions between several signalling systems. Opioids play an important role, as a lack of either enkephalin or β -endorphin in mice abolishes the reinforcing property of food, regardless of the palatability of the food tested. This reinforcing effect is lost in the fasted state, indicating that homeostatic mechanisms can override the hedonistic mechanisms (Hayward *et al.* 2002). In man, opiate antagonists are found to reduce food palatability without reducing subjective hunger (Yeomans *et al.* 1990, Drewnowski *et al.* 1992).

The dopaminergic system is integral to reward-induced feeding behaviour. The influence of central dopamine signalling on feeding is thought to be mediated by the D₁ and D₂ receptors (Schneider 1989, Kuo 2002). Mice which lack dopamine, due to the absence of the tyrosine hydroxylase gene, have fatal hypophagia. Dopamine replacement, by gene therapy, into the caudate putamen restores feeding, whereas replacement into the caudate putamen or nucleus accumbens restores preference for a palatable diet (Szczycka *et al.* 2001).

The nucleus accumbens is an important component of reward circuitry. Injections of opioid agonists and dopamine agonists into this region preferentially stimulate the ingestion of highly palatable foods such as sucrose and fat (Zhang & Kelley 2000, Zhang *et al.* 2003). Conversely, opioid receptor antagonists injected into the nucleus accumbens reduce the ingestion of sucrose rather than less palatable substances (Zhang *et al.* 2003). The reciprocal GABA-ergic connections between the nucleus accumbens and LHA may mediate hedonistic feeding by disinhibition of LHA neurons (Stratford & Kelley 1999). The MCH neurons in the LHA may reciprocally influence the reward circuitry, as the nucleus accumbens is a site which expresses MCH receptors (Saito *et al.* 2001).

Other systems, including those mediated by endocannabinoids and serotonin, may also be able to modulate both reward circuitry and homeostatic mechanisms controlling feeding. Endocannabinoids in the hypothalamus may maintain food intake via CB1 receptors, which co-localize with CART, MCH and orexin peptides (Cota *et al.* 2003). Defective leptin signalling is associated with high hypothalamic endocannabinoid levels in animal models (Di *et al.* 2001). CB1 receptors are also present on adipocytes where they appear to act directly in order to increase lipogenesis (Cota *et al.* 2003). CB1 receptor antagonists are currently in phase III clinical trials, and have been found to reduce appetite and body weight in humans (for a review see Black 2004). Serotonin may directly influence the melanocortin pathway in the ARC

via 5-hydroxytryptamine receptors (Heisler *et al.* 2002). See Figure 3.

Peripheral signals of adiposity

Leptin Leptin (Greek: thin) is a peptide hormone, secreted from adipose tissue, which influences energy homeostasis, immune and neuroendocrine function. Restriction of food intake, over a period of days, results in a suppression of leptin levels, which can be reversed by refeeding (Frederich *et al.* 1995, Maffei *et al.* 1995) or administration of insulin (Saladin *et al.* 1995). Production of leptin correlates positively with adipose tissue mass (Maffei *et al.* 1995). Circulating leptin levels thus reflect both energy stores and food intake. Exogenous leptin replacement decreases fast-induced hyperphagia (Ahima *et al.* 1996), and chronic peripheral administration of leptin to wild-type rodents results in reduced food intake, loss of body weight and fat mass (Halaas *et al.* 1995).

In addition to its effects on appetite, circulating leptin levels also affect energy expenditure in rodents (Halaas *et al.* 1995, Pelleymounter *et al.* 1995), the hypothalamo-pituitary control of the gonadal, adrenal and thyroid axes (Ahima *et al.* 1996, Chehab *et al.* 1996) and the immune response (Lord *et al.* 1998). A replacement dose of leptin is able to reverse the starvation-induced changes of the neuroendocrine axes in both rodents (Ahima *et al.* 1996) and humans (Chan *et al.* 2003). Thus, leptin signalling is able to integrate the body's response to a decrease in energy stores.

Leptin is a product of the *ob* gene expressed predominantly by adipocytes (Zhang *et al.* 1994) but also at lower levels in gastric epithelium (Bado *et al.* 1998) and placenta (Masuzaki *et al.* 1997). A mutation in the *ob* gene, resulting in the absence of circulating leptin, leads to the hyperphagic obese phenotype of the *ob/ob* mouse, which can be normalized by the administration of leptin (Campfield *et al.* 1995, Halaas *et al.* 1995, Pelleymounter *et al.* 1995). Similarly, mutations resulting in the absence of leptin in humans cause severe obesity and hypogonadism (Montague *et al.* 1997, Strobel *et al.* 1998), which can be ameliorated with recombinant leptin therapy in both children (Farooqi *et al.* 1999) and adults (Licinio *et al.* 2004). There is a higher prevalence of obesity than expected in humans with heterozygous leptin deficiency, compared with controls. These subjects also have a greater percentage of body fat, but a lower than expected leptin level (Farooqi *et al.* 2001). Studies from animal models also demonstrate that one deficient copy of the leptin gene can affect body weight (Chung *et al.* 1998, Coleman 1979).

The leptin receptor has a single transmembrane domain and is a member of the cytokine receptor family (Tartaglia *et al.* 1995). The leptin receptor (Ob-R) has multiple isoforms which result from alternative mRNA splicing and post-translational processing (Chua *et al.* 1997, Tartaglia 1997). The different splice forms of the receptor can

Figure 3 The central control of appetite. AP, area postrema; ME, median eminence; NAc, nucleus accumbens; PFA, perifornical area.

be divided into three classes: long, short and secreted (Tartaglia 1997, Ge *et al.* 2002). The long - form Ob-Rb receptor differs from the other forms of the receptor by having a long intracellular domain, which is necessary for the action of leptin on appetite (Lee *et al.* 1996). This intracellular domain binds to Janus kinases (JAK) (Lee *et al.* 1996) and to STAT3 (signal transduction and activators of transcription 3) transcription factors (Vaisse *et al.* 1996) required for signal transduction. The JAK/STAT pathway induces expression of a suppressor of cytokine signalling-3 (SOCS-3), one of a family of cytokine-inducible inhibitors of signalling.

Obesity in the *db/db* mouse is the result of a mutation within the intracellular portion of the Ob-Rb receptor, which prevents signalling (Chen *et al.* 1996, Lee *et al.* 1996). Similarly, mutations within the human leptin receptor result in early-onset morbid obesity, though less severe than that seen with leptin deficiency, and a failure to undergo puberty (Clement *et al.* 1998).

Circulating leptin is transported across the blood-brain barrier via a saturable process (Banks *et al.* 1996). Regulation of transport may be an important modulator of the effects of leptin on food intake. Starvation reduces transport, whereas refeeding increases the transport of leptin

across the blood-brain barrier (Kastin & Pan 2000). The short forms of the receptor have been proposed to have a role in the transport of leptin across the blood-brain barrier (El Haschimi *et al.* 2000), whereas the secreted form is thought to bind to circulating leptin thus modulating its biological activity (Ge *et al.* 2002).

The Ob-Rb receptor is expressed within the hypothalamus (particularly ARC, VMH, DMH and LHA) (Fei *et al.* 1997, Elmquist *et al.* 1998a). Ob-Rb mRNA is expressed in the ARC by NPY/AgRP neurons (Mercer *et al.* 1996) and POMC/CART neurons (Cheung *et al.* 1997). The orexigenic NPY/AgRP neurons are inhibited by leptin, and therefore activated in conditions of low circulating leptin (Stephens *et al.* 1995, Schwartz *et al.* 1996, Hahn *et al.* 1998, Elias *et al.* 1999). Conversely, leptin activates anorexigenic POMC/CART neurons (Schwartz *et al.* 1997, Thornton *et al.* 1997, Kristensen *et al.* 1998, Cowley *et al.* 2001). The anorexic response of leptin is attenuated by administration of an MC4R antagonist, demonstrating that the melanocortin pathway is perhaps an important downstream mediator of leptin signalling (Seeley *et al.* 1997). Mice lacking leptin signalling in POMC neurons are mildly obese and hyperleptinaemic, but less so than mice with a complete deletion of

the leptin receptor (Balthasar *et al.* 2004). This suggests that POMC are important, but not essential, for leptin signalling *in vitro*.

The PVN, LHA VMH and medial preoptic area may be direct targets for leptin signalling as leptin receptors are found in these nuclei (Hakansson *et al.* 1998). Chronic hypothalamic over-expression of the leptin gene, using a recombinant adeno-associated virus vector, has demonstrated distinct actions of leptin in different hypothalamic nuclei. Leptin over-expression in the ARC, PVN and VMH results in a reduction of food intake and energy expenditure, whereas leptin over-expression in the medial preoptic area results in reduced energy expenditure alone (Bagnasco *et al.* 2002).

The NTS, like the ARC, contains leptin receptors (Mercer *et al.* 1998) and leptin administration to the fourth ventricle results in a reduction in food intake and body-weight gain (Grill & Kaplan 2002). Peripheral administration of leptin also results in neuronal activation within the NTS (Elmqvist *et al.* 1997, Hosoi *et al.* 2002). Thus leptin appears to exert its effect on appetite via both the hypothalamus and brainstem.

Although a small subset of obese human subjects have a relative leptin deficiency, the majority of obese animals and humans have a proportionally high circulating leptin (Maffei *et al.* 1995, Considine *et al.* 1996), suggesting leptin resistance. Indeed, recombinant leptin administered subcutaneously to obese human subjects has only shown a modest effect on body weight (Heymsfield *et al.* 1999, Fogtelloo *et al.* 2003). Administration of peripheral leptin to rodents with diet-induced obesity fails to result in a reduction in food intake, although these rodents retain the capacity to respond to icv leptin (Van Heek *et al.* 1997). Exogenous leptin in mice is transported across the blood-brain barrier less rapidly in obese animals (Banks *et al.* 1999). Leptin resistance may be the result of a signalling defect in leptin-responsive hypothalamic neurons, as well as impaired transport into the brain. Resistance to the effects of leptin has been shown to develop in NPY neurons following chronic central leptin exposure (Sahu 2002). Furthermore, the magnitude of hypothalamic STAT3 activation in response to icv leptin is reduced in rodents with diet-induced obesity (El Haschimi *et al.* 2000). Leptin upregulates expression of SOCS-3 in hypothalamic nuclei expressing the Ob-Rb receptor. SOCS-3 acts as a negative regulator of leptin signalling. Therefore, increased or excessive SOCS-3 expression may be an important mechanism for obesity-related leptin resistance. Consistent with this, neuron-specific conditional SOCS-3-knockout mice are resistant to diet-induced obesity (Mori *et al.* 2004). Mice with heterozygous SOCS-3 deficiency are also resistant to obesity and demonstrate both enhanced weight loss and increased hypothalamic leptin receptor signalling in response to exogenous leptin administration (Howard *et al.* 2004). Although as yet untested, SOCS-3 suppression may

be a potential target for the treatment of leptin-resistant obesity.

Leptin resistance seems to occur as a result of obesity, but a lack of sensitivity to circulating leptin may also contribute to the aetiology of obesity. Leptin sensitivity can predict the subsequent development of diet-induced obesity when rodents are placed on a high-energy diet (Levin & Dunn-Meynell 2002). Furthermore, it may be that the high-fat diet itself induces leptin resistance prior to any change in body composition, as rodents on a high-fat diet rapidly demonstrate an attenuated response to leptin administration before they gain weight (Lin *et al.* 2001).

Although leptin deficiency has profound effects on body weight, the effect of high leptin levels seen in obesity are much less potent at restoring body weight. Thus, leptin may be primarily important in periods of starvation, and have a lesser role in times of plenty.

Insulin Insulin is a major metabolic hormone produced by the pancreas and the first adiposity signal to be described (Schwartz *et al.* 1992a). Like leptin, levels of plasma insulin vary directly with changes in adiposity (Bagdade *et al.* 1967) so that plasma insulin increases at times of positive energy balance and decreases at times of negative energy balance (Woods *et al.* 1974). Levels of insulin are determined to a great extent by peripheral insulin sensitivity, and this is related to total body fat stores and fat distribution, with visceral fat being a key determinant of insulin sensitivity (Porte *et al.* 2002). However, unlike leptin, insulin secretion increases rapidly after a meal, whereas leptin levels are relatively insensitive to meal ingestion (Polonsky *et al.* 1988).

Insulin penetrates the blood-brain barrier via a saturable, receptor-mediated process, at levels which are proportional to the circulating insulin (Baura *et al.* 1993). Recent findings suggest that little or no insulin is produced in the brain itself (Woods *et al.* 2003, Banks 2004). Once insulin enters the brain, it acts as an anorexigenic signal, decreasing intake and body weight. An infusion of insulin into the lateral cerebral ventricles in primates (Woods *et al.* 1979) or third ventricle in rodents (Ikeda *et al.* 1986) results in a dose-dependent decrease in food intake and, over a period of weeks, decreases body weight. Injections of insulin directly into the hypothalamic PVN also decrease food intake and rate of weight gain in rats (Menendez & Atrens 1991). Consistent with these data, an injection of antibodies to insulin into the VMH of rats increases food intake (Strubbe & Mein 1977) and repeated antiserum injections increase food intake and rate of weight gain (McGowan *et al.* 1992). Thus, the VMH and PVN seem therefore to play an important part in the ability of centrally administered insulin to reduce food intake.

Male mice with neuron-specific deletion of the insulin receptor in the CNS are obese and dyslipidaemic with increased peripheral levels of insulin (Bruning *et al.* 2000).

Reduction of insulin receptor proteins in the medial ARC, by administration of an antisense RNA directed against the insulin receptor precursor protein, results in hyperphagia and increased fat mass (Obici *et al.* 2002).

i.c.v. administration of an insulin mimetic dose-dependently reduces food intake and body weight in rats, and alters the expression of hypothalamic genes known to regulate food intake and body weight (Air *et al.* 2002). Treatment of mice with orally available insulin mimetics decreases the weight gain produced by a high-fat diet as well as adiposity and insulin resistance (Air *et al.* 2002).

If insulin elicits changes in feeding behaviour at the level of the hypothalamus, then levels of circulating insulin should reflect the effect of centrally administered insulin. Studies of systemic insulin administration have been complicated by the fact that increasing circulating insulin causes hypoglycaemia which in itself potently stimulates food intake. Experiments where glucose levels have been controlled in the face of elevated plasma insulin levels have indeed shown a reduction in food intake in both rodents and baboons (Nicolaidis & Rowland 1976, Woods *et al.* 1984). Thus peripheral and central data are consistent with the insulin system acting as an endogenous controller of appetite.

The insulin receptor is composed of an extracellular α -subunit which binds insulin, and an intracellular β -subunit which transduces the signal and has intrinsic tyrosine kinase activity. The insulin receptor exists as two splice variants resulting in subtype A, with higher affinity for insulin and more widespread expression, and subtype B with lower affinity and expression in classical insulin-responsive tissues such as fat, muscle and liver. There are several insulin receptor substrates (IRSs) including IRS-1 and IRS-2, both identified in neurons (Baskin *et al.* 1994, Burks *et al.* 2000). The phenotype of IRS-1-knockout mice does not show differences in food intake or body weight (Araki *et al.* 1994), but that of IRS-2-knockout mice is associated with an increase in food intake, increased fat stores and infertility (Burks *et al.* 2000). IRS-2 mRNA is highly expressed in the ARC, suggesting that neuronal insulin may be coupled to IRS-2 (Burks *et al.* 2000). There is also evidence to suggest that insulin and leptin, along with other cytokines, share common intracellular signalling pathways via IRS and the enzyme phosphoinositide 3-kinase, resulting in downstream signal transduction (Niswender *et al.* 2001, Porte *et al.* 2002).

Insulin receptors are widely distributed in the brain, with highest concentrations found in the olfactory bulbs and the hypothalamus (Marks *et al.* 1990). Within the hypothalamus, there is particularly high expression of insulin receptors in the ARC; they are also present in the DMH, PVN, and suprachiasmatic and periventricular regions (Corp *et al.* 1986). This is consistent with the hypothesis that peripheral insulin acts on hypothalamic nuclei to control energy homeostasis.

The mechanisms by which insulin acts as an adiposity signal remain to be fully elucidated. Earlier studies pointed to hypothalamic NPY as a potential mediator of the regulatory effects of insulin. i.c.v. administration of insulin during food deprivation in rats prevents the fasting-induced increase in hypothalamic levels of both NPY in the PVN and NPY mRNA in the ARC (Schwartz *et al.* 1992b). NPY expression is increased in insulin-deficient, streptozocin-induced diabetic rats and this effect is reversed with insulin therapy (Williams *et al.* 1989, White *et al.* 1990). More recently, the melanocortin system has been implicated as a mediator of insulin's central actions. Insulin receptors have been found on POMC neurons in the ARC (Benoit *et al.* 2002). Administration of insulin into the third ventricle of fasted rats increases POMC mRNA expression and the reduction of food intake caused by i.c.v. injection of insulin is blocked by a POMC antagonist (Benoit *et al.* 2002). Furthermore, POMC mRNA is reduced by 80% in rats with untreated diabetes, and this can be attenuated by peripheral insulin treatment which partially reduces the hyperglycaemia (Sipols *et al.* 1995). Taken together, these experiments suggest that both the NPY and melanocortin systems are important downstream targets for the effects of insulin on food intake and body weight.

Adiponectin Adiponectin is a complement-like protein, secreted from adipose tissue, which is postulated to regulate energy homeostasis (Scherer *et al.* 1995). The plasma concentration of adiponectin is inversely correlated with adiposity in rodents, primates and humans (Hu *et al.* 1996, Arita *et al.* 1999, Hotta *et al.* 2001). Adiponectin is significantly increased after food restriction in rodents (Berg *et al.* 2001) and after weight loss induced by a calorie-restricted diet (Hotta *et al.* 2000) or gastric partition surgery in obese humans (Yang *et al.* 2001). Peripheral administration of adiponectin to rodents has been shown to attenuate body-weight gain, by increased oxygen consumption, without affecting food intake (Berg *et al.* 2001, Fruebis *et al.* 2001, Yamauchi *et al.* 2001). The effect of peripheral adiponectin on energy expenditure seems to be mediated by the hypothalamus, since adiponectin induced expression of the early gene *c-fos* in the PVN, and may involve the melanocortin system (Qi *et al.* 2004). It is perhaps counterintuitive for a factor that increases energy expenditure to increase following weight loss; however, reduced adiponectin could perhaps contribute to the pathogenesis of obesity.

Studies show that plasma adiponectin levels correlate negatively with insulin resistance (Hotta *et al.* 2001), and treatment with adiponectin can reduce body-weight gain, increase insulin sensitivity and decrease lipid levels in rodents (Berg *et al.* 2001, Yamauchi *et al.* 2001, Qi *et al.* 2004). Adiponectin-knockout mice demonstrate severe diet-induced insulin resistance (Maeda *et al.* 2002) and a propensity towards atherosclerosis in response to intimal

injury (Kubota *et al.* 2002). Thus adiponectin, as well as increasing energy expenditure, may also provide protection against insulin resistance and atherogenesis.

In addition to leptin and adiponectin, adipose tissue produces a number of factors which may influence adiposity. Resistin is an adipocyte-derived peptide which appears to act on adipose tissue to decrease insulin resistance. Circulating resistin levels are increased in rodent models of obesity (Steppan *et al.* 2001) and fall after weight loss in humans (Valsamakis *et al.* 2004). Although resistin may be a mechanism through which obesity contributes to the development of diabetes (Steppan *et al.* 2001), the role of resistin in the pathogenesis of obesity remains to be defined.

Peripheral signals from the gastrointestinal tract

Ghrelin Ghrelin is an orexigenic factor released primarily from the oxyntic cells of the stomach, but also from duodenum, ileum, caecum and colon (Date *et al.* 2000a, Sakata *et al.* 2002). It is a 28-amino-acid peptide with an acyl side chain, *n*-octanoic acid, which is essential for its actions on appetite (Kojima *et al.* 1999). In humans on a fixed feeding schedule, circulating ghrelin levels are high during a period of fasting, fall after eating (Ariyasu *et al.* 2001, Cummings *et al.* 2001, Tschop *et al.* 2001) and are thought to be regulated by both calorie intake and circulating nutritional signals (Tschop *et al.* 2000, Sakata *et al.* 2002). Ghrelin levels fall in response to the ingestion of food or glucose, but not following ingestion of water, suggesting that gastric distension is not a regulator (Tschop *et al.* 2000). In rats, ghrelin shows a bimodal peak, which occurs at the end of the light and dark periods (Murakami *et al.* 2002). In humans, ghrelin levels vary diurnally in phase with leptin, which is high in the morning and low at night (Cummings *et al.* 2001).

An increase in circulating ghrelin levels may occur as a consequence of the anticipation of food, or may have a physiological role in initiating feeding. Administration of ghrelin, either centrally or peripherally, increases food intake and body weight and decreases fat utilization in rodents (Tschop *et al.* 2000, Wren *et al.* 2001a). Furthermore, central infusion of anti-ghrelin antibodies in rodents inhibits the normal feeding response after a period of fasting, suggesting that ghrelin is an endogenous regulator of food intake (Nakazato *et al.* 2001). Human subjects who receive ghrelin intravenously demonstrate a potent increase in food intake of 28% (Wren *et al.* 2001b), and rising pre-prandial levels correlate with hunger scores in humans initiating meals spontaneously (Cummings *et al.* 2004). The severe hyperphagia seen in Prader–Willi syndrome is associated with elevated ghrelin levels (Cummings *et al.* 2002a), and the fall in plasma ghrelin concentration after bariatric surgery, despite weight loss, is thought to be partly responsible for the suppression of appetite and weight loss seen after these operations (Cummings *et al.* 2002b). However, one study has failed to show a corre-

lation between the ghrelin level and the spontaneous initiation of a meal in humans (Callahan *et al.* 2004), and an alteration of feeding schedule in sheep has been shown to modify the timing of ghrelin peaks (Sugino *et al.* 2002). Thus ghrelin secretion may be a conditioned response which occurs to prepare the metabolism for an influx of calories. Whatever the precise physiological role of ghrelin, it appears not to be an essential regulator of food intake, as ghrelin-null animals do not have significantly altered body weight or food intake on a normal diet (Sun *et al.* 2003).

Plasma ghrelin levels are inversely correlated with body mass index. Anorexic individuals have high circulating ghrelin which falls to normal levels after weight gain (Otto *et al.* 2001). Obese subjects have a suppression of plasma ghrelin levels which normalize after diet-induced weight loss (Cummings *et al.* 2002b, Hansen *et al.* 2002). Unlike lean individuals, obese subjects do not demonstrate the same rapid post-prandial drop in ghrelin levels (English *et al.* 2002), which may result in increased food intake and contribute to obesity. Variations within the ghrelin gene may contribute to early-onset obesity (Korbonits *et al.* 2002, Miraglia *et al.* 2004) or be protective against fat accumulation (Ukkola *et al.* 2002), but the role of ghrelin polymorphisms in the control of body weight continues to be controversial (Hinney *et al.* 2002, Wang *et al.* 2004).

Ghrelin is the endogenous agonist of the growth hormone secretagogue receptor (GHS-R), and stimulates growth hormone (GH) release via its actions on the type 1a receptor in the hypothalamus (Kojima *et al.* 1999, Date *et al.* 2000b, Tschop *et al.* 2000, Wren *et al.* 2000). However, the orexigenic action of ghrelin is independent of its effects on GH (Tschop *et al.* 2000, Shintani *et al.* 2001, Tamura *et al.* 2002). Ghrelin administration does not increase food intake in mice lacking GHS-R type 1a, suggesting that the orexigenic effects may be mediated by this receptor; however, these mice have normal appetite and body composition (Chen *et al.* 2004a, Sun *et al.* 2004). This lack of a phenotype suggests that ghrelin receptor antagonists may not be an effective therapy for obesity. GHS-R type 1a is found in the hypothalamus, pituitary myocardium, stomach, small intestine, pancreas, colon, adipose tissue, liver, kidney, placenta and peripheral T-cells (Date *et al.* 2000a, 2002a, Gualillo *et al.* 2001, Hattori *et al.* 2001, Murata *et al.* 2002). Some studies have also described ghrelin analogues which show dissociation between the feeding effects and stimulation of GH, suggesting that GHS-R type 1a may not be the only receptor mediating the effects of ghrelin on food intake (Torsello *et al.* 2000).

Ghrelin is thought to exert its orexigenic action via the ARC of the hypothalamus. c-Fos expression increases within ARC NPY-synthesizing neurons after peripheral administration of ghrelin (Wang *et al.* 2002), and ghrelin fails to increase food intake following ablation of the ARC (Tamura *et al.* 2002). Studies of knockout mice demonstrate that both NPY and AgRP signalling mediate

the effect of ghrelin, although neither neuropeptide is obligatory (Chen *et al.* 2004a). GHS-R are also found on the vagus nerve (Date *et al.* 2002b), and administration of ghrelin leads to c-Fos expression in the area postrema and NTS (Nakazato *et al.* 2001, Lawrence *et al.* 2002), suggesting that the brainstem may also participate in ghrelin signalling.

Ghrelin is also expressed centrally, in a group of neurons adjacent to the third ventricle, between the dorsomedial hypothalamic nucleus (DMH), VMH, PVN and ARC. These neurons terminate on NPY/AgRP, POMC and corticotrophin-releasing hormone neurons, and are able to stimulate the activity of ARC NPY neurons, forming a central circuit which could mediate energy homeostasis (Cowley *et al.* 2003). The central ghrelin neurons also terminate on orexin-containing neurons within the LHA (Toshinai *et al.* 2003), and icv administration of ghrelin stimulates orexin-expressing neurons (Lawrence *et al.* 2002, Toshinai *et al.* 2003). The feeding response to centrally administered ghrelin is attenuated after administration of anti-orexin antibody and in orexin-null mice (Toshinai *et al.* 2003).

PP-fold peptides The PP-fold peptides include PYY, PP and NPY. They all share significant sequence homology and contain several tyrosine residues (Conlon 2002). They have a common tertiary structure which consists of an α -helix and polyproline helix, connected by a β -turn, resulting in a characteristic U-shaped peptide, the PP-fold (Glover *et al.* 1983).

PYY is secreted predominantly from the distal gastrointestinal tract, particularly the ileum, colon and rectum (Adrian *et al.* 1985a, Ekblad & Sundler 2002). The L-cells of the intestine release PYY in proportion to the amount of calories ingested at a meal. Post-prandially, the circulating PYY levels rise rapidly to a plateau after 1–2 h and remain elevated for up to 6 h (Adrian *et al.* 1985a). However, PYY release occurs before the nutrients reach the cells in the distal tract, thus release may be mediated via a neural reflex as well as direct contact with nutrients (Fu-Cheng *et al.* 1997). The levels of PYY are also influenced by meal composition: higher levels are seen following fat intake rather than carbohydrate or protein (Lin & Chey 2003). Other signals, such as gastric acid, CCK and luminal bile salts, insulin-like growth factor 1, bombesin and calcitonin-gene-related peptide increase PYY levels, whereas gastric distension has no effect, and levels are reduced by GLP-1 (Pedersen-Bjergaard *et al.* 1996, Lee *et al.* 1999, Naslund *et al.* 1999a).

Circulating PYY exists in two major forms: PYY_{1–36} and PYY_{3–36}. PYY_{3–36}, the peripherally active anorectic signal, is created by cleavage of the N-terminal Tyr-Pro residues by dipeptidyl peptidase IV (DPP-IV) (Eberlein *et al.* 1989). DPP-IV is involved in the cleavage of multiple hormones including products of the proglucagon gene (Boonacker & Van Noorden 2003).

Administration of PYY causes a delay in gastric emptying, a delay in secretions from the pancreas and stomach, and increases the absorption of fluids and electrolytes from the ileum after a meal (Allen *et al.* 1984, Adrian *et al.* 1985b, Hoentjen *et al.* 2001). Peripheral administration of PYY_{3–36} to rodents has been shown to inhibit food intake, reduce weight gain (Batterham *et al.* 2002, Challis *et al.* 2003) and improve glycaemic control in rodent models of diabetes (Pittner *et al.* 2004). The effect on appetite may be dependent on a minimization of environmental stress, which in itself can result in a decrease in food intake (Halatchev *et al.* 2004). Acute stress has been shown to activate the NPY system (Conrad & McEwen 2000, Makino *et al.* 2000), which may render the system insensitive to the inhibitory effect of PYY_{3–36}, resulting in masking of the anorectic effect of the peptide.

Intravenous administration of PYY_{3–36} to normal-weight human subjects also has potent effects on appetite, resulting in a 30% reduction in food intake (Batterham *et al.* 2002, 2003a). The reduction in calories is accompanied by a reduction in subjective hunger without an alteration in gastric emptying. This effect persists for up to 12 h after the infusion is terminated, despite circulating PYY_{3–36} returning to basal levels (Batterham *et al.* 2002). Thus, PYY_{3–36} may be physiologically important as a post-prandial satiety signal.

Obese human subjects have a relatively low circulating PYY and a relative deficiency of post-prandial secretion (Batterham *et al.* 2003a), although these subjects retain sensitivity to exogenous administration. Obese patients treated by jejunoileal bypass surgery (Naslund *et al.* 1997) or vertical-banded gastroplasty (Alvarez *et al.* 2002) have elevated PYY levels, which may contribute to their appetite loss. Thus long-term administration of PYY_{3–36} could be an effective obesity therapy. After chronic peripheral administration of PYY_{3–36}, rodents do indeed demonstrate reduced weight gain (Batterham *et al.* 2002).

PP is produced by cells at the periphery of the islets of the endocrine pancreas, and to a lesser extent in the exocrine pancreas, colon and rectum (Larsson *et al.* 1975). The release of PP occurs in proportion to the number of calories ingested, and levels remain elevated for up to 6 h post-prandially (Adrian *et al.* 1976). The release of PP is biphasic, with the contribution of the smaller first phase increasing with consecutive meals, although the total release remains proportional to the caloric load (Track *et al.* 1980). The circulating levels of PP are increased by gastric distension, ghrelin, motilin and secretin (Christofides *et al.* 1979, Mochiki *et al.* 1997, Peracchi *et al.* 1999, Arosio *et al.* 2003) and reduced by somatostatin (Parkinson *et al.* 2002). There is also a background diurnal rhythm, with circulating PP low in the early hours of the morning and highest in the evening (Track *et al.* 1980). The levels of PP have been found to reflect long-term energy stores, with lower levels (Lassmann *et al.* 1980, Glaser *et al.* 1988) and reduced second phase of release (Lassmann *et al.* 1980) in

obese subjects, and higher levels in anorexic subjects (Uhe *et al.* 1992, Fujimoto *et al.* 1997). However, conflicting studies have found no difference between lean and obese subjects (Wisén *et al.* 1992), or between obese subjects before and after weight loss (Meryn *et al.* 1986).

Peripheral administration of PP reduces food intake, body weight and energy expenditure, and ameliorates insulin resistance and dyslipidaemia in rodent models of obesity (Malaisse-Lagae *et al.* 1977, Asakawa *et al.* 2003). However, it has been suggested that obese rodents are less sensitive to the effects of PP than normal-weight rodents (McLaughlin & Baile 1981). Transgenic mice that over-express PP also have a lean phenotype with reduced food intake (Ueno *et al.* 1999).

Normal-weight human volunteers given an infusion of PP demonstrate decreased appetite, and a 25% reduction in food intake over the following 24 h (Batterham *et al.* 2003b). Unlike rodents, humans do not seem to have altered gastric emptying in response to PP (Adrian *et al.* 1981). Further investigation of the administration of PP to obese subjects may indicate whether it could be an effective therapy for obesity. PP does appear to be an efficacious treatment for hyperphagia secondary to Prader–Willi syndrome. These patients have blunted basal and post-prandial PP responses which may contribute to their hyperphagia and obesity (Zipf *et al.* 1981, 1983). A twice-daily ‘replacement’ of PP by infusion results in a 12% reduction in food intake during the therapy (Berntson *et al.* 1993).

The PP-fold family bind to Y_1 – Y_5 receptors, which are seven-transmembrane-domain, G-protein-coupled receptors (Larhammar 1996). The receptors differ in their distribution and are classified according to their affinity for PYY, PP and NPY. Whereas NPY and PYY bind with high affinity to all Y receptors, PYY_{3–36} shows high affinity for Y_2 and some affinity for Y_1 and Y_5 receptors. PP binds with greatest affinity to Y_4 and Y_5 receptors (Larhammar 1996).

The N-terminal of PYY allows it to cross the blood–brain barrier freely from the circulation, whereas PP cannot (Nonaka *et al.* 2003). It is thought that the effect of peripheral PYY_{3–36} on appetite may be mediated by the arcuate Y_2 receptor, a pre-synaptic inhibitory receptor expressed on NPY neurons (Broberger *et al.* 1997). Electrophysiological studies have shown that administration of PYY_{3–36} inhibits NPY neurons (Batterham *et al.* 2002), and NPY mRNA expression levels are reduced after peripheral PYY_{3–36} administration (Batterham *et al.* 2002, Challis *et al.* 2003). The anorectic effect of PYY_{3–36} is abolished in Y_2 receptor-knockout mice and reduced by a selective Y_2 agonist (Batterham *et al.* 2002). Inhibition of NPY neurons also results in increased activity with the POMC neurons which may contribute to reduced food intake. Immunohistochemical studies have demonstrated that peripherally administered PYY_{3–36} induces *c-fos* expression (Batterham *et al.* 2002,

Halatchev *et al.* 2004) and POMC mRNA expression (Challis *et al.* 2003) in ARC POMC neurons. However, the melanocortin system does not appear to be obligatory for the effects of PYY_{3–36} on appetite, as PYY_{3–36} continues to be effective in MC4R-knockout mice (Halatchev *et al.* 2004) and POMC-null mice (Challis *et al.* 2004). Recently, it has been suggested that CART may mediate the effect of PYY_{3–36} on appetite (Coll *et al.* 2004). The peripheral administration of PYY_{3–36} has also been shown to decrease ghrelin levels (Batterham *et al.* 2003a), and this effect on circulating gut hormone levels may also contribute to its effect on appetite.

In contrast to peripheral PYY_{3–36}, the central actions of PYY_{1–36} and PYY_{3–36} are orexigenic. PYY administered into the third, lateral or fourth cerebral ventricles (Clark *et al.* 1987, Corpa *et al.* 2001), into the PVN (Stanley *et al.* 1985) or into the hippocampus (Hagan *et al.* 1998) potently stimulates food intake in rodents. This orexigenic effect is reduced in both Y_1 and Y_5 receptor-knockout mice (Kanatani *et al.* 2000). Therefore these lower-affinity receptors may mediate the central feeding effect of PYY_{3–36}, whereas peripheral PYY_{3–36} is able to access the higher-affinity ARC Y_2 receptors (Batterham *et al.* 2002).

Circulating PP is unable to cross the blood–brain barrier, but may exert its anorectic effect on the ARC via the area postrema (Whitcomb *et al.* 1990). This effect may occur via the Y_5 receptor as there is no response in Y_5 receptor-knockout mice, although the anorectic effect is not reduced by Y_5 receptor antisense oligonucleotides (Katsuura *et al.* 2002). Following the peripheral administration of PP, the expression of hypothalamic NPY and orexin mRNA is significantly reduced (Asakawa *et al.* 2003). PP may also exert some anorectic action via the vagal pathway to the brainstem, as vagotomy seems to reduce its efficacy (Asakawa *et al.* 2003). Like PYY_{3–36}, PP is also able to reduce gastric ghrelin mRNA expression, and this has been postulated to mediate its efficacy in the treatment of hyperphagia secondary to Prader–Willi syndrome (Asakawa *et al.* 2003). Thus PP sends anorectic signals via brainstem pathways, hypothalamic neuropeptides and by modulating expression of other gut hormones such as ghrelin. In contrast to the peripheral effects, when administered centrally into the third ventricle PP causes increased food intake (Clark *et al.* 1984). However, the mechanism of this orexigenic effect following central injection is unclear.

Proglucagon products The proglucagon gene product is expressed in the L-cells of the small intestine, pancreas and central nervous system. A small group of neurons expressing pre-proglucagon are present in the NTS (Tang-Christensen *et al.* 2001). The enzymes prohormone convertase 1 and 2 cleave proglucagon into different products depending on the tissue (Holst 1999). In the pancreas, glucagon is the major product, whereas in the

brain and intestine oxyntomodulin (OXM) and GLP-1 and GLP-2 are the major products.

The L-cells of the small intestine release GLP-1 in response to nutrients (Herrmann *et al.* 1995). Central administration of GLP-1, into the third or fourth ventricles and into the PVN, reduces acute calorie intake (Turton *et al.* 1996), and decreases weight gain when given chronically to rodents (Meeran *et al.* 1999). Peripheral administration also inhibits food intake and activates c-Fos in the brainstem (Tang-Christensen *et al.* 2001, Yamamoto *et al.* 2003). Thus, GLP-1 may influence energy homeostasis via the brainstem pathways.

In humans, intravenous administration of GLP-1 decreases food intake in both lean and obese individuals in a dose-dependent manner (Verdich *et al.* 2001a). However, the effect is small when infusions achieve post-prandial circulating levels (Flint *et al.* 2001, Verdich *et al.* 2001b). Some evidence suggests GLP-1 secretion is reduced in obese subjects (Holst *et al.* 1983, Ranganath *et al.* 1996, Naslund *et al.* 1999b) and weight loss normalizes the levels (Verdich *et al.* 2001b). Obese subjects, given subcutaneous GLP-1 prior to each meal, reduce their calorie intake by 15% and lose 0.5 kg in weight over 5 days (Naslund 2003). Reduced secretion of GLP-1 could therefore contribute to the pathogenesis of obesity and replacement may restore satiety.

In addition to its effect on appetite, GLP-1 is an incretin hormone (Kreymann *et al.* 1987), and potentiates all steps of insulin biosynthesis (MacDonald *et al.* 2002). GLP-1 has been found to normalize blood glucose levels, in poorly controlled type 2 diabetes, during both a short-term intravenous infusion (Nauck *et al.* 1993) and after a 6-week subcutaneous infusion (Zander *et al.* 2002). Body weight was also reduced by 2 kg after the subcutaneous infusion (Zander *et al.* 2002). GLP-1 is broken down rapidly by the enzyme DPP-IV resulting in a short half-life in the circulation. However, resistant albumin-bound GLP-1, exendin-4 (a naturally occurring peptide from the lizard *Heloderma*) and inhibitors of the enzyme DPP-IV are all currently in development for the treatment of diabetes (see the review by Holst 2004). Although GLP-1 may be useful in type 2 diabetic patients, it has been reported to cause hypoglycaemia in non-diabetic subjects (Todd *et al.* 2003), which could limit its usefulness as an obesity therapy.

OXM is released from the L-cells of the small intestine in proportion to nutrient ingestion (Ghatei *et al.* 1983, Le Quellec *et al.* 1992), and shows a diurnal variation with lowest values early in the morning, rising to a peak in the evening (Le Quellec *et al.* 1992). Administration of OXM centrally or peripherally acutely inhibits food intake in rodents (Dakin *et al.* 2001, 2004), and chronic administration via these routes results in reduced body weight gain and adiposity (Dakin *et al.* 2002, 2004). OXM may also increase energy expenditure, as OXM-treated animals lose more weight than pair-fed animals, an effect which is

postulated to be mediated by the thyroid axis (Dakin *et al.* 2002). An infusion of OXM to normal-weight human subjects reduces hunger and decreases calorie intake by 19–3%, an effect which persists up to 12 h post-infusion (Cohen *et al.* 2003). Anorexia occurs in human conditions associated with high OXM levels, such as tropical sprue (Besterman *et al.* 1979) and jejunoileal bypass surgery (Holst *et al.* 1979, Sarson *et al.* 1981). Thus OXM may be a physiological regulator of energy homeostasis. However, the circulating concentrations of OXM in obese subjects and its potential to decrease weight in humans remain unknown.

It has been suggested that the effects of GLP-1 and OXM on energy homeostasis are mediated by the GLP-1 receptor. The anorexigenic effects of GLP-1 and OXM are blocked by the antagonist, exendin(9–39), when administered centrally (Turton *et al.* 1996, Dakin *et al.* 2001). GLP-1 receptors are present in both the NTS and hypothalamus (Uttenthal *et al.* 1992, Shughrue *et al.* 1996), and are also widespread in the periphery: in the pancreas, lung, brain, kidney, gastrointestinal tract and heart (Wei & Mojsov 1995, Bullock *et al.* 1996).

The effect of OXM on appetite may not simply be mediated via GLP-1 receptors. Peripheral administration of OXM results in increased c-Fos in the ARC, but not in the brainstem region (Dakin *et al.* 2004), a pattern of neuronal activation which is different from that seen with GLP-1. Furthermore, the affinity of OXM for GLP-1 receptor is approximately two orders of magnitude less than that of GLP-1 yet they appear to be similarly efficacious at reducing food intake (Fehmann *et al.* 1994). Although exendin(9–39) can block the appetite effects of centrally administered OXM and GLP-1, antagonist administered into the ARC is able to abolish the effect of peripheral OXM, but not peripheral GLP-1. There may thus be distinct receptors mediating the physiological effects of the two peripheral gut hormones. The peripheral administration of OXM reduces circulating ghrelin by 20% in rodents (Dakin *et al.* 2004) and 44% in human subjects (Cohen *et al.* 2003), an effect which is also likely to contribute to its effects on appetite.

CCK CCK is found predominantly in the duodenum and jejunum, although it is widely distributed in the gastrointestinal tract (Larsson & Rehfeld 1978). It is present in multiple bioactive forms, including CCK-58, CCK-33 and CCK-8, all derived from the same gene product (Reeve *et al.* 1994). CCK is rapidly released locally and into the circulation in response to nutrients, and remains elevated for up to 5 h (Liddle *et al.* 1985). CCK is also found within the brain where it functions as a neurotransmitter involved in diverse processes such as reward behaviour, memory and anxiety, as well as satiety (Crawley & Corwin 1994).

CCK coordinates digestion by stimulating the release of enzymes from the pancreas and gall bladder, increasing

Figure 4 Peripheral control of appetite.

intestinal motility and inhibiting gastric emptying (Liddle *et al.* 1985, Moran & Schwartz 1994). Administration of CCK, to both humans and animals, has long been known to inhibit food intake by reducing meal size and duration (Gibbs *et al.* 1973, Kissileff *et al.* 1981), an effect which is enhanced by gastric distension (Kissileff *et al.* 2003). Although CCK exerts its effect on food intake rapidly, its duration of action is brief. It has a half-life of only 1–2 min, and it is not effective at reducing meal size if the peptide is administered more than 15 min before a meal (Gibbs *et al.* 1973). In animals, chronic pre-prandial administration of CCK does reduce food intake, but is seen to increase meal frequency, with no resulting effect on body weight (West *et al.* 1984, West *et al.* 1987). A continuous infusion of CCK becomes ineffective after the first 24 h (Crawley & Beinfeld 1983). Thus, the efficacy of CCK as a potential treatment for human obesity is in doubt.

CCK exerts its effect via binding to CCK_A and CCK_B receptors; these are G-protein-coupled receptors with seven transmembrane domains (Wank *et al.* 1992a). CCK_A receptors are found throughout the brain, including areas such as the NTS, DMH and area postrema. Peripherally, CCK_A receptors are found in the pancreas, on vagal afferent and enteric neurons. CCK_B receptors are

also distributed widely in the brain, are present in the afferent vagus nerve, and are found within the stomach (Moran *et al.* 1986, 1990, Wank *et al.* 1992a, 1992b).

The CCK_A receptor subtype is thought to mediate the effect of the endogenous agonist on appetite (Asin *et al.* 1992). Suppression of food intake is only seen in response to the sulphated form of CCK which binds with high affinity to CCK_A receptors (Gibbs *et al.* 1973). Furthermore, administration of a CCK_A receptor antagonist increases calorie intake and reduces satiety (Hewson *et al.* 1988, Beglinger *et al.* 2001).

Circulating CCK sends satiety signals via activation of vagal fibres (Schwartz & Moran 1994, Moran *et al.* 1997). The action of CCK on the vagal nerve may partly be a paracrine or neurocrine effect, as there is evidence that locally released CCK may activate vagal fibres without a significant increase in plasma CCK level (Reidelberger & Solomon 1986). The vagal nerve projects to the NTS, which in turn relays information to the hypothalamus (Schwartz *et al.* 2000). Peripheral CCK may act both on the vagal nerve and directly on the CNS by crossing the blood–brain barrier (Reidelberger *et al.* 2003). Evidence from the CCK_A receptor-knockout (OLETF) rat suggests that CCK may act on the DMH to suppress NPY levels

(Bi *et al.* 2001). This is supported by data which demonstrate that administration of CCK to the DMH inhibits food intake significantly (Blevins *et al.* 2000).

CCK may also act as a longer-term indicator of nutritional status: the CCK_A receptor-knockout (OLETF) rat (but not the CCK_A receptor-knockout mouse) is hyperphagic and obese (Moran *et al.* 1998, Schwartz *et al.* 1999). Chronic administration of both CCK antibodies and CCK_A antagonists also results in weight gain in rodent models, although not with a significant increase in food intake (McLaughlin *et al.* 1985, Meereis-Schwanke *et al.* 1998). The long-term effect of CCK on body weight may partially result from an interaction with signals of adiposity such as leptin, which enhance the satiating effect of CCK (Matson *et al.* 2000). See Figure 4.

Future direction

The brain integrates peripheral signals of nutrition in order to maintain a stable body weight. However, in some individuals, genetic and environmental factors interact to result in obesity. Understanding of the complex system which regulates energy homeostasis is progressing rapidly, enabling new obesity therapies to emerge. Available pharmacological agents, such as sibutramine and orlistat, have limited efficacy and are restricted to 1 or 2 years of therapy respectively (see review by Finer 2002). Currently, the only obesity treatment in clinical use that has shown significant long-term weight loss is gastrointestinal bypass surgery (Frandsen *et al.* 1998, Mitchell *et al.* 2001). However, because of its complications, this procedure is restricted to patients with morbid obesity. Post-surgical weight loss is not caused by malabsorption, but is due to a loss of appetite (Atkinson & Brent 1982), which may be secondary to elevated PYY and OXM (Sarson *et al.* 1981, Naslund *et al.* 1997) and/or suppressed ghrelin levels (Cummings *et al.* 2002b). This suggests that therapies based on these hormones may be effective in the long term, without the need for surgical intervention. As mechanisms of disordered energy homeostasis are clarified, treatments based on peripheral hormones or central neuropeptide signals could be tailored to the individual; just as leptin deficiency is treated successfully with leptin replacement. Therapeutic strategies may thus significantly impact on the enormous morbidity and mortality associated with obesity, as even modest weight loss can reduce the risk of diabetes, cancer and cardiovascular disease.

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