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Peripheral tissue–brain interactions in the regulation of food intake

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More than 70 years ago the glucostatic, lipostatic and aminostatic hypotheses proposed that the central nervous system sensed circulating levels of different metabolites, changing feeding behaviour in response to the levels of those molecules. In the last 20 years the rapid increase in obesity and associated pathologies in developed countries has involved a substantial increase in the knowledge of the physiological and molecular mechanisms regulating body mass. This effort has resulted in the recent discovery of new peripheral signals, such as leptin and ghrelin, as well as new neuropeptides, such as orexins, involved in body-weight homeostasis. The present review summarises research into energy balance, starting from the original classical hypotheses proposing metabolite sensing, through peripheral tissue–brain interactions and coming full circle to the recently-discovered role of hypothalamic fatty acid synthase in feeding regulation. Understanding these molecular mechanisms will provide new pharmacological targets for the treatment of obesity and appetite disorders.

Food intake regulation: Gastrointestinal signals: Adipose and pancreatic hormones: Neural control

The prevalence of overweight and obesity in most developed countries has increased strikingly during the last 30 years (Friedman, 2000, 2003; Flier, 2004; Farooqi & O'Rahilly, 2005). Body weight depends on the balance between energy intake and energy consumption. Despite wide daily variation in food intake and energy expenditure, for most individuals body weight remains extremely stable over long periods of time. For this stability to occur, feeding and energy expenditure must be constantly modulated and balanced. Obesity results when the former exceeds the latter and there is an accumulation of an excess of fat in peripheral tissues such as white adipose tissue, which is specifically adapted for this function, liver and muscle, which results in metabolic disease (Friedman, 2000, 2003; Flier, 2004; Farooqi & O'Rahilly, 2005). Obesity has a profound impact on human health and lifespan. Being obese correlates not just with associated metabolic dysfunction such as type 2 diabetes and CVD, but is also associated with the occurrence of certain cancers (Calle & Kaaks, 2004).

The first hypotheses proposed to explain the periphery–brain interaction in the regulation of food intake were the glucostatic, lipostatic and aminostatic hypotheses. These models proposed that circulating factors, e.g. lipids (lipostatic hypothesis), glucose (glucostatic hypothesis) or protein products (aminostatic hypothesis), that are generated in proportion to body fat stores and/or nutritional status act as signals to the brain, eliciting changes in energy intake and expenditure (Campfield *et al*. 1996). The current 'obesity epidemic' has driven forward research efforts in the investigation of body-weight homeostasis. For this reason, in the last decade there has been a major increase in the knowledge of the physiological and molecular mechanism regulating body mass. Animals are now known to regulate body weight by a complex homeostatic mechanism involving interactions between peripheral organs and the central nervous system (CNS). Peripheral organs, such as white adipose tissue, gut, thyroid, muscle and gonads produce signals that inform brain centres of the nutritional, as well as metabolic, status of the animal

Abbreviations: AgRP, agouti-related peptide; ARC, arcuate nucleus of the hypothalamus; BBB, blood–brain barrier; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; CB, cannabinoids; CNS, central nervous system; DMH, dorsomedial nucleus of the hypothalamus; EC, endocannabinoids; FAS, fatty acid synthase; GHS-R, growth hormone secretagogue receptor; GLP, glucagon-like peptide; NPY, neuropeptide Y; LHA, lateral hypothalamic area; MCH, melanin-concentrating hormone; MC*n*R, melanocortin receptor (*n* 1–5); NTS, nucleus of the solitary tract; OB-Ra–f, isoforms of leptin receptor; OX, orexin; OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PVH, paraventricular nucleus of the hypothalamus; PYY, peptide YY; VMH, ventromedial nucleus of the hypothalamus.

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(Flier, 2004; Horvath *et al*. 2004; Abizaid *et al*. 2006; Morton *et al*. 2006). The CNS receives and integrates this entire signalling system, adjusting energy intake (food intake) and energy expenditure, according to the demands of the organism.

The present review summarises the current knowledge about periphery–brain interactions in the regulation of feeding. A full understanding of these mechanisms will allow the establishment of effective therapies to counter eating disorders and obesity.

Gastrointestinal signals regulating food intake

In addition to its evident function in the digestion and absorption of nutrients, the gut and associated organs (liver, pancreas and visceral white adipose tissue depots) play an important role in the control of energy homeostasis, particularly in the short-term regulation of food intake. Both the enteric nervous system and gut hormones are known to control the initiation and termination of individual meals (Halford & Blundell, 2000*a*; Badman & Flier, 2005; Perez-Tilve *et al*. 2006).

Enteric nervous system

The gastrointestinal tract receives a dual extrinsic innervation from the autonomic nervous system via its parasympathetic (cholinergic) division, which includes vagal and pelvic nerves, and its sympathetic (noradrenergic) division, which comprises splanchnic nerves. Parasympathetic innervation is mainly inhibitory, and sympathetic innervation is mainly excitatory. In addition to this autonomic innervation, the gastrointestinal tract also has its own nervous system, i.e. the enteric nervous system (Konturek *et al*. 2004; Badman & Flier, 2005), which is involved in every aspect of gut function, from mastication to defaecation. Besides these roles, the enteric nervous system is also implicated in gastric and pancreatic exocrine secretion, gut motility, blood supply and hormone release (Konturek *et al*. 2004; Badman & Flier, 2005).

The enteric nervous system projects to the CNS through vagal and sympathetic (spinal) nerves. These projections transmit a variety of information to several CNS areas, including mechanical stimuli (distension, contraction), chemical stimuli (presence of nutrients in the gut lumen) and neurohumoral stimuli (gut hormones, neurotransmitters and neuromodulators; Langley, 1994; Konturek *et al*. 2004). Most of these afferent vagal fibres terminate in the nucleus of the solitary tract (NTS) in the brainstem, and in laminas I and V of the dorsal horn of spinal cord (Maggi, 1991; Konturek *et al*. 2004). Some signals from the gut are transmitted from the NTS to higher neural centres, such as the paraventricular (PVH) and arcuate (ARC) nuclei of the hypothalamus (Berthoud *et al*. 1990), the bed nucleus of the stria terminallis and the ventral thalamus. The integration of all these afferent signals related to food presence in the gut regulates the size of individual meals (Flier, 2004; Konturek *et al*. 2004; Badman & Flier, 2005).

Gut hormones

Cholecystokinin. Despite the profuse development of the enteric nervous system, the main route of communication between the brain and the gut in relation to energy homeostasis is via the circulation. One of the hormones first identified in regulating energy homeostasis was the gastrointestinal hormone cholecystokinin (CCK), which is secreted by I cells in the duodenum and the jejunum into the circulation in response to nutrient ingestion (protein and fatty acids; Larsson & Rehfeld, 1978; Bray, 2000; Halford & Blundell, 2000*a*; Badman & Flier, 2005; Stanley *et al*. 2005; Perez-Tilve *et al*. 2006). CCK exists in several molecular forms, the major forms in the plasma being CCK-8, -33 and -39 (Halford & Blundell, 2000*a*; Konturek *et al*. 2004; Stanley *et al*. 2005). Once secreted, CCK reduces meal size and duration in both man and animals (Gibbs *et al*. 1973; Kissileff *et al*. 1981; Smith *et al*. 1981*a*; Pi-Sunyer *et al*. 1982; Muurahainen *et al*. 1988) and infusion of a CCK antagonist increases energy intake in human subjects (Beglinger *et al*. 2001). However, despite its anorectic actions, repeated administration of CCK does not influence body weight because although meal frequency is increased, there is no overall change in feeding (West *et al*. 1984; Wei & Mojsov, 1995). Thus, CCK is mostly involved in the short-term control of food intake, together with distension of the upper gastrointestinal tract (Konturek *et al*. 2004; Badman & Flier, 2005).

CCK signals via two distinct G-protein-coupled receptors termed CCK_A and CCK_B (Wank *et al*. 1992*a*; Halford & Blundell, 2000*a*). Both receptors are widely expressed in the CNS and in the periphery (Moran *et al*. 1986, 1990; Wank *et al*. 1992*a*,*b*). The effect of CCK on food intake is mediated via CCK_A (Asin *et al*. 1992; Halford & Blundell, 2000*a*). CCK crosses the brain–blood barrier (BBB; Reidelberger *et al*. 2004) and acts on neuropeptide Y (NPY) neurons in the dorsomedial nucleus of the hypothalamus (DMH), as well as the NTS in the brainstem (Moran *et al*. 1997; Bi *et al*. 2001). The effects of CCK on feeding are also mediated through paracrine and neuroendocrine activation of vagal fibres (Reidelberger & Solomon, 1986; Schwartz & Moran, 1994; Moran *et al*. 1997).

Glucagon-like peptide-1 and oxyntomodulin. The preproglucagon gene product yields two important satiety peptides, glucagon-like peptide (GLP)-1 and oxyntomodulin (OXM; Tang-Christensen *et al*. 2001; Stanley *et al*. 2005). The preproglucagon gene is widely expressed in the gut, the pancreas and the NTS in the brainstem. Tissue-specific processing of preproglucagon by prohormone convertases 1 and 2 produces different products: glucagon is the main product in the pancreas; GLP-1 and -2 and OXM are the major products in CNS and gut (Tang-Christensen *et al*. 2001; Badman & Flier, 2005; Stanley *et al*. 2005).

GLP-1 and OXM are released from L cells in response to NEFA and carbohydrates (Ghatei *et al*. 1983; Le Quellec *et al*. 1992; Herrmann *et al*. 1995; Hirasawa *et al*. 2005). Both peptides inhibit feeding when they are centrally or peripherally administrated (Turton *et al*. 1996;

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Dakin *et al*. 2004), and chronic administration of GLP-1 and OXM decreases weight gain and adiposity in rodents (Meeran *et al*. 1999; Dakin *et al*. 2004). The actions of both GLP-1 and OXM on feeding may be mediated via the GLP-1 receptor, which is expressed in the hypothalamus, brainstem and periphery (Uttenthal *et al*. 1992; Wei & Mojsov, 1995; Shughrue *et al*. 1996; Bullock *et al*. 1996). The anorectic effect of GLP-1 and OXM is also present in man (Flint *et al*. 1998, 2000, 2001; Gutzwiller *et al*. 1999; Naslund *et al*. 1999; Verdich *et al*. 2001; Meier *et al*. 2002). Despite this evidence, it has been reported that some of the anorectic effects of GLP-1 may be related to taste aversion and visceral illness (Shughrue *et al*. 1996; Bullock *et al*. 1996; Thiele *et al*. 1997; Yamamoto *et al*. 2002). Regardless of the anorectic actions of GLP-1 and OXM reported in rodents, GLP-1 receptor-knock-out mice have normal feeding behaviour (Scrocchi *et al*. 1996, 1997, 2000).

Preproglucagon also yields GLP-2. The role of GLP-2 has not been fully established; however, central administration reduces feeding, probably via GLP-1 receptor (Badman & Flier, 2005). No effect of GLP-2 on feeding has been reported in man (Schmidt *et al*. 2003).

Peptide YY. Peptide YY (PYY) is secreted postprandially by the L cells of the gastrointestinal tract, especially in the most distal portions such as the ileum, colon and rectum; PYY secretion is correlated with energy intake (Stanley *et al*. 2005). There are two main forms of PYY in the circulation: $PYY_{1–36}$ and $PYY_{3–36}$ (Grandt *et al*. 1994; Batterham *et al*. 2002; Wynne *et al*. 2004; Stanley *et al*. 2005). Peripheral administration of PYY has several actions, including delaying gastric emptying and gastric secretion, and increasing ileum absorption. It has also been reported that peripheral administration of $PYY_{3–36}$ inhibits food intake and reduces weight gain in rodents, primates and man (Batterham *et al*. 2002; Challis *et al*. 2003; Moran *et al*. 2005). PYY crosses the BBB and probably exerts its actions via the presynaptic Y_2 receptor of NPY neurons in the ARC, releasing inhibition of pro-opiomelanocortin (POMC) neurons and consequently inhibiting feeding (Broberger *et al*. 1997; Batterham *et al*. 2002; Challis *et al*. 2003).

Despite this evidence, the anorectic effect of $PYY_{3–36}$ is controversial and not easily duplicated (Tschop *et al*. 2004; Coll *et al*. 2004*a*). Indeed, in contrast to peripheral injection, central administration of both $PYY_{1–36}$ and $PYY_{3–36}$ stimulates feeding in rodents (Stanley *et al*. 1985; Clark *et al*. 1987; Hagan *et al*. 1998; Corpa *et al*. 2001). It has also been suggested that the anorexic effect of PYY may be partially mediated by an aversive response (Halatchev & Cone, 2005).

Bombesin. Bombesin is a peptide that is widely distributed in the mammalian gut. Plasma levels of bombesin increase markedly after food intake (Gibbs *et al*. 1979; Wynne *et al*. 2004), and peripheral and central administration of bombesin is anorectic (Gibbs *et al*. 1979; Smith *et al*. 1981*b*). Bombesin is structurally very similar to gastrin-releasing peptide and neuromedin B, and binds to their receptors. Additionally, a bombesin-3 receptor has been cloned (Ladenheim *et al*. 1997). Knocking out bombesin-3 receptor induces moderate hyperphagia, obesity and metabolic alterations in mice (Ohki-Hamazaki *et al*. 1997).

Gastric inhibitory polypeptide. Gastric inhibitory polypeptide is secreted from the duodenal K cells, predominantly in response to ingested fat. Mice fed a high-fat diet have increased levels of gastric inhibitory polypeptide together with obesity (Wynne *et al*. 2004; Badman & Flier, 2005), whereas mice lacking the gastric inhibitory polypeptide receptor are protected against obesity induced by both a high-fat diet and leptin deficiency (*ob/ob* mice; Miyawaki *et al*. 2002). Thus, gastric inhibitory polypeptide may be involved in the development of obesity in response to high fat intake.

Ghrelin. Ghrelin is a twenty-eight-amino acid acylated hormone mainly synthesised and secreted by the gut in the gastric oxyntic cells (A/X cells) at the fundus of the stomach, as well as the duodenum, ileum, caecum and colon (Kojima *et al*. 1999; Date *et al*. 2000; Gualillo *et al*. 2001; Sakata *et al*. 2002). Ghrelin expression has also been detected in other tissues, such as the hypothalamus (Kojima *et al*. 1999; Horvath *et al*. 2001; Cowley *et al*. 2003) testis (Barreiro *et al*. 2002; Tena-Sempere *et al*. 2002), pituitary (Caminos *et al*. 2003*a*), ovary (Caminos *et al*. 2003*b*; Gaytan *et al*. 2003), heart (Iglesias *et al*. 2004) and placenta (Gualillo *et al*. 2001).

Ghrelin, which was initially identified as the endogenous ligand of the growth hormone secretagogue receptor (GHS-R), exerts a potent and specific growth hormone-releasing activity *in vitro* (Kojima *et al*. 1999) and *in vivo* (Arvat *et al*. 2000; Seoane *et al*. 2000), as well as increasing the transcription rate of the Pit-1 gene (García *et al*. 2001). Further studies have led to the recognition that ghrelin also plays an important role in energy homeostasis. Ghrelin administration induces positive energy balance in rodents by decreasing fat utilisation without markedly changing energy expenditure or locomotor activity (Wren *et al*. 2000; Nakazato *et al*. 2001). Furthermore, peripheral and central administration of ghrelin to rodents increases feeding, as well as fat mass, and reduces fat utilisation (Tschop *et al*. 2000; Nakazato *et al*. 2001; Wren *et al*. 2001*b*; Seoane *et al*. 2003). Plasma levels of ghrelin are regulated by food intake, rising during fasting and immediately before meals, and falling after food intake (Ariyasu *et al*. 2001; Cummings *et al*. 2001; Tschop *et al*. 2001*a*). These changes in ghrelin expression are directly modulated by energy intake and nutritional signals such as blood glucose and ingestion of fat or carbohydrate (Tschop *et al*. 2000; Sakata *et al*. 2002). For this reason a physiological role of ghrelin in meal initiation has been proposed (Cummings *et al*. 2001; Cummings & Shannon, 2003). This suggestion is supported by experiments (Nakazato *et al*. 2001) that use anti-ghrelin antibodies to block the actions of ghrelin, which results in an attenuation of fasting-induced refeeding.

The effects of ghrelin on feeding and growth hormone secretion are mediated via type 1a GHS-R (Kojima *et al*. 1999; Tschop *et al*. 2000; Chen *et al*. 2004; Sun *et al*. 2004). However, the orexigenic effects of ghrelin are independent of growth hormone-releasing properties (Tschop *et al*. 2000; Shintani *et al*. 2001; Tamura *et al*. 2002). The expression of GHS-R in the hypothalamus is

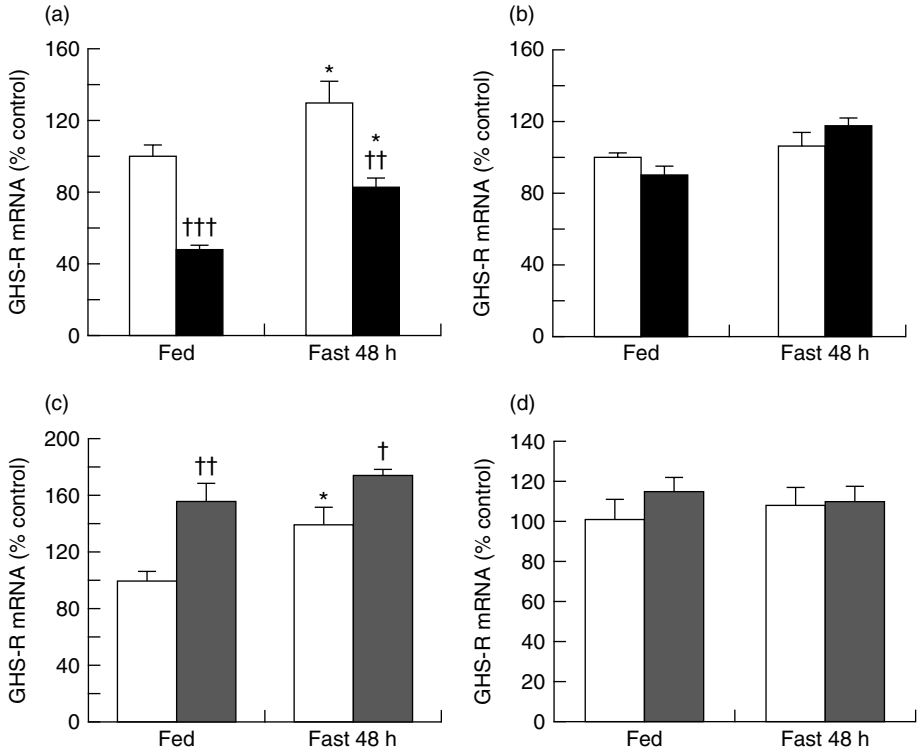

Fig. 1. Regulation of growth hormone secretogogue receptor (GHS-R) in the rat hypothalamus by leptin and ghrelin. Effects of intracerebroventricular leptin (■; a, b) and ghrelin (▩; c, d) on GHS-R expression in the arcuate nucleus (a, c) and the ventromedial nucleus of the hypothalamus (b, d) in fed and 48 h-fasted rats. (□), Vehicle. Values are means with their standard errors represented by vertical bars. Mean values were significantly different from the corresponding values for fed rats: *$P<0{\cdot}05$. Mean values were significantly different from the corresponding values for vehicle-fed or vehicle-48 h-fasted rats: †$P<0{\cdot}05$, ††$P<0{\cdot}01$, †††$P<0{\cdot}001$.

nutritionally regulated in a nucleus-specific manner, with fasting increasing the mRNA levels of GHS-R in the ARC but not in the ventromedial nucleus of the hypothalamus (VMH). Additionally, the level of GHS-R expression in the ARC, but not in the VMH, is reduced by leptin and increased by ghrelin in a growth hormone-dependent fashion (Fig. 1; Nogueiras *et al*. 2004*b*).

Ghrelin is also important in the regulation of energy homeostasis in man. Intravenous administration of ghrelin to healthy volunteers increases food intake (Wren *et al*. 2001*a*). Moreover, the rise in preprandial ghrelin correlates with hunger scores in human subjects eating spontaneously (Cummings *et al*. 2004). Interestingly, the levels of ghrelin are correlated with adiposity in man, with an inverse relationship between plasma ghrelin levels and BMI (Tschop *et al*. 2001*b*). Obese human subjects show reduced levels of plasma ghrelin, which rise to normal after diet-induced weight loss (Hansen *et al*. 2002; Cummings *et al*. 2002*b*). Moreover, in obese individuals the postprandial regulation of ghrelin seems to be altered, which may be related to continuous food intake and/or obesity (English *et al*. 2002). Finally, the severe hyperphagia seen in patients with Prader-Willi syndrome is associated with elevated ghrelin levels, in contrast to other forms of obesity in which ghrelin levels are low (Cummings *et al*. 2002*a*).

In the CNS the action of ghrelin on feeding is mainly exerted via the ARC. GHS-R mRNA is expressed in neurons in the ARC co-expressing NPY and agouti-related peptide (AgRP; Guan *et al*. 1997; Tannenbaum *et al*. 1998; Willesen *et al*. 1999; Zigman *et al*. 2006), and the central administration of ghrelin increases the mRNA content of NPY and AgRP in the ARC in fed and fasting conditions (Kamegai *et al*. 2001; Nakazato *et al*. 2001; Seoane *et al*. 2003). There is also some evidence that orexin (also termed hypocretin; OX) neurons in the lateral hypothalamic area (LHA; Lawrence *et al*. 2002; Toshinai *et al*. 2003) and neurons in the NTS and the area postrema in the brainstem may mediate the orexigenic actions of ghrelin (Nakazato *et al*. 2001; Lawrence *et al*. 2002). Recent data also indicate that ghrelin acts in the hypothalamus by altering fatty acid metabolism and AMP-activated protein kinase. It has been demonstrated that ghrelin increases hypothalamic AMP-activated protein kinase phosphorylation levels, activating it. This action may be associated to specific changes in hypothalamic neuropeptides, although the exact molecular mechanisms and anatomical details of this interaction have not been fully identified (Andersson *et al*. 2004; Kola *et al*. 2005).

Despite ghrelin having a potent action in regulating food intake, both ghrelin-knock-out mice and mice lacking GHS-R type 1a have normal feeding patterns and body composition on a standard diet (Sun *et al*. 2003). However, on a high-fat diet the absence of ghrelin (Wortley *et al*. 2005) or the ghrelin receptor (Zigman *et al*. 2005) protects

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against early-onset obesity; in both cases this reduced weight gain is associated with decreased adiposity and increased energy expenditure and locomotor activity. These data suggest that ghrelin, like leptin, may play an important role in the development of hypothalamic systems regulating energy balance (Grove & Cowley, 2005). Very interestingly, elimination of ghrelin improves the diabetic phenotype but not the obese phenotype of *ob/ob* mice (Sun *et al*. 2006).

Finally, it has recently been reported that obestatin, a new peptide derived from the ghrelin gene, inhibits food intake by acting through the orphan receptor GPR39 (Nogueiras & Tschop, 2005; Zhang *et al*. 2005). Despite this evidence there are some discrepancies in relation to the anorectic effect of obestatin (Nogueiras *et al*. 2006) as well as its binding to GPR39 (Holst *et al*. 2006). If the anorectic effect is confirmed, this finding could provide a new drug target for the treatment of obesity.

Adipose tissue hormones

Originally thought of as an inert tissue involved in the storage of energy, it is now clear that adipose tissue is an active endocrine organ (Casanueva & Diéguez, 1999; Ahima & Flier, 2000*a*). Adipocyte hormones regulate appetite, glucose homeostasis, lipid metabolism, endocrine function, cardiovascular physiology, reproduction, immune function and development, amongst other functions (Casanueva & Diéguez, 1999; Ahima & Flier, 2000*a*; Pinto *et al*. 2004; Horvath & Diano, 2004).

Leptin

Among the adipocyte hormones, the one that has most changed the concept of white adipose tissue as an inert tissue is leptin, the product of the *ob* (obese) gene (Zhang *et al*. 1994). Leptin is expressed principally in adipocytes (Zhang *et al*. 1994), but also at lower levels in the gastrointestinal tract (Bado *et al*. 1998) and placenta (Señarís *et al*. 1997; Masuzaki *et al*. 1997). Plasma leptin levels reflect both energy stores and acute energy balance. Circulating leptin levels are tightly correlated with adipose tissue mass (Maffei *et al*. 1995), and food restriction results in suppression of circulating leptin (Frederich *et al*. 1995; Maffei *et al*. 1995), which can be reversed by refeeding or insulin administration. Peripheral and central leptin administration reduces spontaneous and fasting-induced hyperphagia (Ahima *et al*. 1996; Ahima, 2000), and chronic peripheral administration reduces feeding, resulting in loss of fat mass and body weight (Halaas *et al*. 1995).

The complete lack of leptin seen in the *ob/ob* mouse has profound consequences on body-weight homeostasis, leading to hyperphagia and obesity, as well as neuroendocrine and immune dysregulation, which is normalised by leptin administration (Campfield *et al*. 1995; Halaas *et al*. 1995; Pelleymounter *et al*. 1995). In man leptin deficiency causes morbid obesity and hypogonadism (Montague *et al*. 1997; Strobel *et al*. 1998), which can be improved by recombinant leptin (Farooqi *et al*. 1999; Licinio *et al*. 2004). In the same way, defective leptin receptor signalling also has a profound impact on body weight and endocrine function. A point mutation in the intracellular domain of the long isoform of the leptin receptor (OB-Rb) gene, which prevents signalling, results in obesity in *db/db* mice (Chen *et al*. 1996; Lee *et al*. 1996). Defects in the human leptin receptor have also been reported; as with leptin deficiency, these subjects have hypogonadism and early-onset morbid obesity (Clement *et al*. 1998, 2002).

Leptin binds and activates a receptor of the cytokine receptor family (Tartaglia *et al*. 1995). Alternative mRNA splicing and post-translational processing results in several isoforms of the receptor (OB-Ra, OB-Rb, OB-Rc, OB-Re and OB-Rf; Tartaglia, 1997; Chua *et al*. 1997; Ahima & Flier, 2000*b*). OB-Rb is the variant implicated in signal transduction (Tartaglia, 1997; Ahima & Flier, 2000*b*). The other isoforms may act as leptin sequesters and transporters, binding leptin without signal transduction (Friedman & Halaas, 1998; Ahima & Flier, 2000*b*). Ob-Rb possesses a long intracellular domain that binds to janus kinases (Lee *et al*. 1996) and to signal transducer and activator of transcription-3 transcription factors (Vaisse *et al*. 1996; Hakansson *et al*. 1999), resulting in signal transduction and mediating the action of leptin on feeding (Lee *et al*. 1996). Activation of the janus kinases/signal transducers and activators of transcription pathway induces expression of suppressor of cytokine signalling-3, a cytokine-inducible inhibitor of signalling; suppressor of cytokine signalling-3 expression is up regulated by leptin in hypothalamic nuclei expressing the Ob-Rb receptor (Ahima & Flier, 2000*b*; Howard *et al*. 2004).

Plasma leptin crosses the BBB via a saturable process (Banks *et al*. 1996; Banks 2001*a*,*b*), thought to be mediated by OB-Ra and OB-Rc (El Haschimi *et al*. 2000; Ahima & Flier, 2000*b*). OB-Rb is widely expressed in the hypothalamus (being most abundant in the ARC, the VMH and the DMH) the LHA and the medial preoptic area (Fei *et al*. 1997; Elmquist *et al*. 1998; Hakansson *et al*. 1998, 1999). OB-Rb is also expressed in feeding-modulating neurons in the brainstem (Elmquist *et al*. 1997; Mercer *et al*. 1998). In the ARC OB-Rb mRNA is expressed by the two major neuronal groups: neurons co-expressing the orexigenic neuropeptides NPY and AgRP (Mercer *et al*. 1996; Cheung *et al*. 1997); a distinct second population of neurons co-expressing the anorexigenic POMC and cocaine- and amphetamine-regulated transcript (CART). Leptin inhibits the activity of orexigenic AgRP/NPY neurons and reduces expression of AgRP and NPY (Stephens *et al*. 1995; Hahn *et al*. 1998; Elias *et al*. 1999), while activating anorectic CART/POMC neurons (Schwartz *et al*. 1997; Kristensen *et al*. 1998; Swart *et al*. 2002). In the LHA leptin receptor is expressed in neurons expressing the orexigenic neuropeptides melanin-concentrating hormone (MCH) and the OX, which are inhibited by leptin (Qu *et al*. 1996; López *et al*. 2000). When leptin levels are low, such as in food restriction and fasting, the expression of orexigenic neuropeptides is increased and orexigenic neurons are activated; in contrast, anorexigenic neuropeptides are decreased and anorexigenic neurons are inhibited. When plasma leptin levels are high, as in the satiated animal, the anorectic pathways are switched on and the

orexigenic pathways are switched off (Friedman & Halaas, 1998; Kalra *et al*. 1999; Saper *et al*. 2002; Flier, 2004).

The role of leptin in human obesity is intriguing. As described earlier, while there are individuals with defects in leptin synthesis or leptin signalling, these cases are extremely rare. The majority of obese individuals are characterised by high levels of leptin (Maffei *et al*. 1995; Considine *et al*. 1996), suggesting leptin insensitivity or resistance; in fact, leptin administration to obese subjects has only a moderate effect on body weight (Heymsfield *et al*. 1999; Fogteloo *et al*. 2003). In rodents diet-induced obesity has also been correlated with the development of leptin resistance (Van Heek *et al*. 1997; Levin & Dunn-Meynell, 2002). Leptin resistance may develop via different mechanisms. Peripheral leptin resistance may be the result of impairment in the function of the saturable leptin transporters in the BBB (Burguera *et al*. 2000; Furuhata *et al*. 2000; Levin *et al*. 2004). Central leptin resistance may develop as a result of impaired leptin signalling via OB-Rb in the hypothalamus, which could be related to a decrease in OB-Rb expression (García *et al*. 2000; Seeber *et al*. 2002; López *et al*. 2005*a*), a defect in the intracellular signalling mechanism of the janus kinases/signal transducers and activators of transcription pathway or the over-expression of suppressor of cytokine signalling-3 (El Haschimi *et al*. 2000; Howard *et al*. 2004; Ladyman & Grattan, 2004; Levin *et al*. 2004; Munzberg *et al*. 2004; Munzberg & Myers, 2005).

The role of leptin in the hypothalamus is not only associated with food-intake regulation. Leptin also contributes to the adaptation of the neuroendocrine axis to fasting (Ahima *et al*. 1996; Casanueva & Diéguez, 1999). Additionally, leptin is a neurotrophic factor during the development of the hypothalamus, mediating neuronal plasticity (Bouret *et al*. 2004*a*,*b*; Bouret & Simerly, 2004; Pinto *et al*. 2004). The importance of this function of leptin in the context of obesity is still not clear, but it has been proposed that perturbations in perinatal nutrition that alter leptin levels may have long-term consequences for the formation and function of hypothalamic circuits regulating feeding and body weight in adulthood (López *et al*. 2005*a*).

Adiponectin

Adiponectin, also termed adipocyte complement-related protein, apM1 or adipoQ, is a 244-amino acid protein secreted from adipose tissue (Hu *et al*. 1996; Berg *et al*. 2002; Tsao *et al*. 2002), the placenta (Caminos *et al*. 2005) and cardiomyocytes (Pineiro *et al*. 2005). Adiponectin has four domains: an amino-terminal signal sequence; a region without homology to other known proteins; a collagen-like region; a carboxy-terminal globular domain. The globular domain forms homotrimers, and additional interactions with collagenous segments cause the formation of higher-molecular-weight complexes (Pajvani *et al*. 2003).

Adiponectin is important in the regulation of energy homeostasis (Scherer *et al*. 1995). Plasma levels of adiponectin are inversely correlated with adiposity in several species, including man (Hu *et al*. 1996; Arita *et al*. 1999; Hotta *et al*. 2001) Adiponectin is increased after food restriction in rodents (Berg *et al*. 2001, 2002). Peripheral administration to rodents has been shown to attenuate body-weight gain, by increased O_2 consumption, without affecting food intake (Berg *et al*. 2001; Fruebis *et al*. 2001; Yamauchi *et al*. 2003). This effect on energy expenditure appears to be mediated by the hypothalamic melanocortin system, without affecting other neuropeptide systems regulated by leptin (Qi *et al*. 2004). Circulating adiponectin levels negatively correlate 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; Winzell *et al*. 2004). Adiponectin-knock-out mice have severe diet-induced insulin resistance (Maeda *et al*. 2002). The mechanism by which adiponectin improves insulin resistance and glucose metabolism is not fully understood, but some of these effects may be mediated by activation of AMP-activated protein kinase (Yamauchi *et al*. 2002).

Adiponectin binds and activates two known membrane receptors, adipoR1 and adipoR2 (Yamauchi *et al*. 2003). AdipoR1 is highly expressed in skeletal muscle; it has a high affinity for the globular domain of adiponectin and low affinity for the full-length ligand. AdipoR2 is highly expressed in the liver and preferentially binds to the full-length ligand. Adiponectin receptors have also been detected in the hypothalamus (Qi *et al*. 2004) and the placenta (Caminos *et al*. 2005). Very interestingly, it has recently been reported that adiponectin does not cross the BBB but modifies cytokine expression in the brain endothelial cells, making unlikely a direct effect of adiponectin in the CNS (Spranger *et al*. 2006).

Resistin

Resistin is produced by adipose tissue and appears to be involved in the modulation of insulin sensitivity and adipocyte differentiation (Steppan *et al*. 2001*a*,*b*; Vidal-Puig & O'Rahilly, 2001; Steppan & Lazar, 2002). In addition to adipose tissue, resistin is also expressed in the stomach, intestine, adrenal gland, testis and skeletal muscle (Nogueiras *et al*. 2003*a*,*b*, 2004*a*).

Resistin expression is regulated in a tissue- and gender-specific manner. Food deprivation leads to a decrease in resistin mRNA expression only in adipose tissue (Nogueiras *et al*. 2003*a*,*b*). Circulating resistin is increased in obese rodents (Steppan *et al*. 2001*a*) and man (Savage *et al*. 2001) and falls after weight loss in man (Valsamakis *et al*. 2004). Resistin-knock-out mice display increased glucose tolerance on a high-fat diet (Banerjee *et al*. 2004; Sul, 2004) and transgenic mice over-expressing a dominant negative form of resistin show increased adiposity with elevated plasma leptin and adiponectin levels, as well as enhanced glucose tolerance and insulin sensitivity (Sul, 2004). All this evidence suggests that resistin may contribute to the development of insulin resistance and diabetes in obesity (Steppan *et al*. 2001*a*,*b*; Vidal-Puig & O'Rahilly, 2001; Steppan & Lazar, 2002). In support of this role, recent evidence has shown that resistin inhibits feeding through a hypothalamic mechanism (Tovar *et al*.

2005). However, the molecular details of that action are not fully established.

IL-6 and IL-1

IL-6 is a multifunctional immune-modulating cytokine that has been suggested to have important functions in glucose and lipid metabolism. IL-6 is secreted from adipose tissue into the circulation, and its expression is positively correlated with BMI and total fat tissue. IL-6-knock-out mice develop obesity, which can partly be reversed by IL-6 replacement, suggesting a role for IL-6 in the long-term regulation of adipose tissue mass (Wallenius *et al*. 2002*b*). Furthermore, central administration of a low dose of IL-6 decreases feeding and increases energy expenditure in rats, suggesting a central site of action for IL-6 (Wallenius *et al*. 2002*a*). Supporting this hypothesis it has also been suggested that IL-6 and IL-6 receptors are expressed in the neurons in the VMH and the DMH (Schobitz *et al*. 1993). IL-1 is also involved in body-weight homeostasis. IL-1 type I receptor-knock-out mice display an obese and insulin-resistant phenotype. This obese phenotype is characterised by a decrease in leptin sensitivity, fat utilisation and locomotor activity (García *et al*. 2006).

Pancreatic hormones

Insulin

Insulin is also an adiposity signal. Plasma insulin concentrations correlate with peripheral insulin sensitivity, which in turn is linked to total body fat depots and fat distribution, visceral fat being a key determinant (Schwartz *et al*. 1992*a*, 2000).

Insulin secretion by the pancreas increases rapidly after a meal, exerting an anorectic effect via the CNS (Schwartz *et al*. 1992*a*, 2000). Insulin enters the CNS via saturable receptor-mediated transport across the BBB (Woods *et al*. 2003). Central administration of insulin or insulin mimetic reduces feeding and body weight in rodents and primates (Woods *et al*. 1979; Schwartz *et al*. 1992*a*, 2000; Air *et al*. 2002). Administration of antisense RNA against the insulin receptor induces hyperphagia and increased fat mass (Obici *et al*. 2002*a*), and neuron-specific deletion of the insulin receptor results in obesity, hyperinsulinaemia and dyslipidaemia in mice (Bruning *et al*. 2000). Insulin receptors are widespread in the brain and occur in hypothalamic nuclei involved in food intake (ARC, DMH, PVH and periventricular nucleus; Corp *et al*. 1986; Marks *et al*. 1990). In the hypothalamus the actions of insulin on food intake and body weight are mediated by NPY (Schwartz *et al*. 1992*b*) and the melanocortin system (Sipols *et al*. 1995; Obici *et al*. 2001; Benoit *et al*. 2002).

Pancreatic polypeptide

Pancreatic polypeptide (PP) belongs to the PP-fold family of peptides, which also includes PYY and NPY (Conlon, 2002). PP is mainly produced by peripheral cells of the islets of Langerhans, the exocrine pancreas and the distal gastrointestinal tract (Small & Bloom, 2004; Stanley *et al*. 2005). Plasma PP concentrations increase proportionally to energy intake (Small & Bloom, 2004; Stanley *et al*. 2005), and they appear to be inversely proportional to adiposity, with high levels in anorexic subjects and reduced levels in obese subjects (Lassmann *et al*. 1980; Fujimoto *et al*. 1997).

Peripheral PP administration reduces feeding and body weight in obese rodents (Malaisse-Lagae *et al*. 1977) and feeding in man (Batterham *et al*. 2003). The anorectic effect of PP is exerted via brainstem pathways (in the area postrema), regulation of hypothalamic neuropeptides (NPY and OX) and modulation of ghrelin expression (Asakawa *et al*. 2003). The anorectic effect of PP is mediated by Y_5 receptor. In contrast to the peripheral actions, central administration of PP increases food intake (Clark *et al*. 1984); the receptors mediating this action and the mechanisms involved are unclear.

Neural control of food intake

Hypothalamic regulation of food intake

The CNS receives information from the sensory experience of eating and also from the process of ingestion, absorption, metabolism and energy storage. The original theories explaining the central control of food intake were based on a 'dual-centre hypothesis' (Hecherington & Ranson, 1942; Anand & Brobeck, 1951). In this model, based on hypothalamic-lesioning experiments, feeding is controlled by two hypothalamic areas: the lateral hypothalamic 'feeding centres' and the ventromedial hypothalamic 'satiety centres'. Lesions of the LHA decrease food intake and eventually lead to starvation and death. Conversely, lesions of several of the mediobasal hypothalamic nuclei result in obesity. Since then, knowledge concerning the hypothalamic regulation of feeding has increased; however, the main concept is the same, i.e. that anatomically-defined hypothalamic areas regulate food intake. These hypothalamic nuclei form interconnected neuronal circuits that respond to changes in energy status by altering the expression of specific neuropeptides, resulting in changes in energy intake and expenditure (Friedman & Halaas, 1998; Kalra *et al*. 1999; Schwartz *et al*. 2000; Saper *et al*. 2002; Flier, 2004; Abizaid *et al*. 2006; Morton *et al*. 2006). Table 1 summarises some hypothalamic neuropeptides and neurotransmitters regulating food intake.

Hypothalamic neuronal pathways regulating appetite

Arcuate nucleus. The ARC is considered as the 'master hypothalamic centre' for feeding control. It is situated around the base of the third ventricle and lies immediately above the median eminence. The ARC–median eminence is a circumventricular organ in which the BBB is modified, allowing the entry of peptides and proteins from the circulation, such as PYY, GLP-1, leptin and insulin (Banks *et al*. 1996; Kastin *et al*. 2002; Nonaka *et al*. 2003; Woods *et al*. 2003).

Two distinct neuronal populations in the ARC integrate peripheral nutritional and/or feeding signals. One set of neurons in the ventromedial part of the ARC express the

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Table 1. Molecules with demonstrated orexigenic and/or anorexigenic effects in some animal models

Orexigenic: feeding stimulators		Anorexigenic: feeding inhibitors	
26RF amide	Somatostatin*	Adiponectin	Neuromedin B
Agouti-related peptide	Thyroid hormones (tri-iodothyronine)	Amylin	Neuromedin S
		Anorectin	Neuromedin U
γ-Aminobutyric acid	VGF (non-acronymic)	Bombesin	Neuropeptide B
Beacon		Brain-derived neurotrophic factor	Neuropeptide K
β-Endorphin		Calcitonin-gene related peptide	Neuropeptide S
Corticosterone		Cocaine- and amphetamine-regulated transcript	Neuropeptide W
Dopamine			
Dynorphin		Cholecystokinin	Neurotensin
Endocannabinoids		Ciliary neurotrophic factor	Obestatin?
Galanin		Corticotrophin-releasing hormone	Oleoylethanolamide
Galanin-like peptide		Enterostatin	Oleoyl-estrone
Growth hormone		Galanin-like peptide	Oxyntomodulin
Growth hormone-releasing hormone		Glucagon-like peptide-1	Oxytocin
		Insulin	Pancreatic polypeptide
Glutamate		Insulin-like growth factors-I and-II	Prolactin-releasing peptide
Ghrelin		IL-1	Peptide $YY_{3–36}$
Melanin-concentrating hormone		IL-6	Resistin
		Long chain fatty acids	Serotonin
Motilin		Leptin	Somatostatin*
Noradrenaline		α-Melanocyte-stimulating hormone	Thyrotrophin-releasing hormone
Neuropeptide Y			
Oestrogens		Nesfatin-1	Urocortin
Orexins (A and B)			

*The effect of somatostatin on food intake has been reported to be contradictory and very dependent of the doses used. Low doses increase feeding and high doses decrease feeding (Feifel & Vaccarino, 1989, 1990, 1994).

orexigenic neuropeptides NPY and AgRP (Broberger *et al*. 1998*b*; Hahn *et al*. 1998). These neurons mostly project to the PVH. In the ventrolateral part of the ARC there is a second population of neurons that express the anorexigenic products of POMC, the precursor of α-melanocyte-stimulating hormone, and also CART (Elias *et al*. 1998*a*; Kristensen *et al*. 1998). This set of neurons projects more broadly within the CNS to hypothalamic nuclei such as the DMH, the LHA and the perifornical area, as well as the PVH. Thus, AgRP/NPY and CART/POMC neurons act as the primary hypothalamic site of action of peripheral hormones such as insulin and leptin. ARC neurons, in turn, project to secondary hypothalamic nuclei ('second order neurons') such as the PVH and the LHA. In these second-order neurons the release of neuropeptides is regulated to modulate energy intake (Schwartz *et al*. 2000; Flier, 2004).

Paraventricular nucleus. The PVH integrates neuropeptide signals from numerous CNS regions, including the ARC and brainstem (Sawchenko & Swanson, 1983). Administration into the PVH of almost all of the known orexigenic and anorexigenic signalling molecules alters appetite (Kalra *et al*. 1999). Furthermore, CART/POMC neurons originating in the ARC potentiate inhibitory γ-aminobutyric acidergic signalling in the PVH and reduce feeding, while AgRP/NPY neurons inhibit this γ-aminobutyric acidergic signalling and stimulate food intake (Cowley *et al*. 1999). Despite the large number of neuropeptides acting on the PVH, recent work suggests that they act to regulate feeding through a common mechanism involving AMP-activated protein kinase (Minokoshi *et al*. 2004).

The PVH also plays a major role in the integration of food intake and neuroendocrine function. AgRP/NPY and CART/POMC neurons in the ARC project to thyrotrophin-releasing hormone neurons in the PVH (Legradi & Lechan, 1999; Fekete *et al*. 2000). AgRP/NPY inhibits pro-thyrotrophin-releasing hormone gene expression (Fekete *et al*. 2002), while α-melanocyte-stimulating hormone stimulates pro-thyrotrophin-releasing hormone expression and inhibits the fasting-induced suppression of thyrotrophin-releasing hormone (Fekete *et al*. 2000). The PVH also contains corticotrophin-releasing hormone neurons, which form reciprocal circuits with NPY neurons in the ARC (Kalra *et al*. 1999).

Ventromedial nucleus of the hypothalamus. The VMH (as distinct from thalamic ventromedial nucleus) has long been considered as the 'satiety centre', since the finding that bilateral lesions in this nucleus induce hyperphagia and obesity (Hecherington & Ranson, 1942; Anand & Brobeck, 1951). The VMH mainly receives projections from AgRP/NPY and CART/POMC neurons in the ARC. Additionally, the VMH neurons project their axons to the ARC, DMH and LHA, as well as brainstem regions such as the NTS (Kalra *et al*. 1999; Pinto *et al*. 2004; Sternson *et al*. 2005).

The VMH has been considered as a 'reception nucleus' for peripheral signals, as well as central signals. VMH neurons show a high abundance of leptin, ghrelin, oestrogen, thyroid hormone and neuropeptide receptors (Shughrue *et al*. 1997; Roselli *et al*. 1997; Kalra *et al*. 1999; Nogueiras *et al*. 2004*b*; King, 2006). However, despite the identification of these receptors, the molecular mechanisms regulating feeding in the VMH have not yet been well

established. Some evidence suggests that brain-derived neurotrophic factor and steroidogenic factor-1 may play crucial roles in mediating body weight in this nucleus. Mice with reduced brain-derived neurotrophic factor receptor expression (Xu *et al*. 2003), and with reduced brain-derived neurotrophic factor signalling (Xu *et al*. 2003), and also steroidogenic factor-1-knock-out mice (Majdic *et al*. 2002), have increased body weight. Furthermore, activation of steroidogenic factor-1 neurons by leptin is required for normal body-weight homeostasis (Dhillon *et al*. 2006). Finally, it has recently been reported that fatty acid synthase (FAS) and malonyl-CoA levels in this nucleus may play an important physiological role in the regulation of feeding (López *et al*. 2006).

Dorsomedial nucleus of the hypothalamus. Like the VMH, the DMH has long been considered to be an integrative centre, processing information from other hypothalamic areas (Kalra *et al*. 1999). The DMH is located immediately dorsal to the VMH and has extensive direct connections with other hypothalamic nuclei (e.g. the PVH and the LHA), as well as the brainstem (Kalra *et al*. 1999; Bellinger & Bernardis, 2002). Destruction of the DMH induces hyperphagia and obesity, although less dramatically than VMH lesions (Bellinger & Bernardis, 2002). Very recent evidence has also demonstrated that the DMH is critical for the expression of food-entrainable circadian rhythms (Gooley *et al*. 2006).

The DMH contains NPY-expressing cell bodies, which are involved in the hyperphagia observed in pregnant and lactating rats (Li *et al*. 1998; García *et al*. 2003). Moreover, CART-expressing neurons are highly abundant in the DMH; the exact function of these cells is unknown, but they are probably involved in fasting-induced responses (Henry *et al*. 2001).

Lateral hypothalamic area. Although the involvement of the LHA, including the perifornical area, in the regulation of feeding has been known for >60 years (Hecherington & Ranson, 1942; Anand & Brobeck, 1951), the molecular mechanisms involved had remained unknown until 15 years ago when MCH was identified as the first orexigenic peptide exclusively expressed in this nucleus (Qu *et al*. 1996). Other neuropeptides important in the regulation of feeding are also highly expressed in this area, such as galanin (Hakansson *et al*. 1998), dynorphin (Chou *et al*. 2001), CART-encoded peptides (Koylu *et al*. 1998) and OX (de Lecea *et al*. 1998; Sakurai *et al*. 1998; López *et al*. 2005*b*).

MCH and prepro-OX are each expressed by a different cell population, both of which receive projections from AgRP/NPY and CART/POMC neurons in the ARC (Broberger *et al*. 1998*a*; Elias *et al*. 1998*b*; Horvath *et al*. 1999). Additionally, both sets of neurons express leptin receptors, indicating that their actions may be integrated (Hakansson *et al*. 1998, 1999). The LHA also contains a large number of glucose-sensing neurons (Bernardis & Bellinger, 1996). OX neurons in the LHA respond to a fall in glucose levels with an increase in activity (Cai *et al*. 1999; Moriguchi *et al*. 1999). LHA neurons project widely to a large number of extrahypothalamic areas. Major targets of the MCH and OX neurons include the brainstem motor systems, sympathetic and parasympathetic preganglionic nuclei in the medulla and spinal cord, the locus coeruleus, the medial raphe nucleus, the tuberomammillary nucleus and the cerebral cortex. All these areas are fundamental in different aspects of food intake regulation, from feeding-related behaviours to arousal and motor activity (Willie *et al*. 2001; López *et al*. 2001*a*, 2005*b*; Saper *et al*. 2002; Steininger *et al*. 2004). Thus, these second-order neurons in the LHA play a fundamental role in integrating information from ARC neurons before sending it to other CNS areas involved in feeding control.

Hypothalamic neuropeptides regulating food intake

Neuropeptide Y. NPY is a thirty-six-amino acid peptide belonging to the PP-fold family of peptides, which also includes PYY and PP (Conlon, 2002). NPY is widely distributed in the CNS and is one of the most potent stimulators of food intake; repeated third ventricle or PVH administration of NPY induces striking hyperphagia and obesity (Stanley *et al*. 1986; Zarjevski *et al*. 1993). Central administration of NPY also reduces brown fat thermogenesis (Billington *et al*. 1991), suppresses sympathetic nerve activity (Egawa *et al*. 1991) and inhibits the thyroid axis (Fekete *et al*. 2002) in order to reduce energy expenditure. Additionally, NPY induces hyperinsulinaemia (Moltz & McDonald, 1985; Zarjevski *et al*. 1993), hypercorticosteronaemia (Zarjevski *et al*. 1993) and reduced plasma testosterone levels (Kalra *et al*. 1999); effects that are independent of increased food intake. NPY mRNA levels and NPY release in the ARC respond to changes in energy status, being increased after fasting and food restriction and decreased after refeeding (Sanacora *et al*. 1990; Kalra *et al*. 1991; Swart *et al*. 2002).

Regardless of its potent orexigenic effect, NPY-knock-out mice show normal body weight and adiposity (Erickson *et al*. 1996), probably related to a compensatory and redundant mechanism in the orexigenic pathways, particularly in relation to AgRP. However, it has been reported recently that selective ablation of AgRP/NPY neurons in adult mice results in hypophagia and leanness, demonstrating direct evidence for a critical role of these neurons in the regulation of energy homeostasis (Gropp *et al*. 2005; Luquet *et al*. 2005).

NPY, as part of the PP-fold family of peptides, binds and activates G-protein-coupled receptors termed Y_1–Y_6 (Larhammar, 1996; Kalra *et al*. 1999). Y_1–Y_5 receptors are present in rat brain, but Y_6 is only active in mice, being absent in rats and inactive in primates (Inui, 1999). The orexigenic action of NPY is thought to be mediated by hypothalamic Y_1, Y_2, Y_4 and Y_5 receptors (Kalra *et al*. 1999; Williams G *et al*. 2000, 2001; Stanley *et al*. 2005).

Melanocortin system (α-melanocyte-stimulating hormone/pro-opiomelanocortin and agouti-related peptide). Among the hypothalamic neuropeptide systems that regulate feeding, melanocortins play a prominent role (Kalra *et al*. 1999; Cone, 1999, 2005; Coll *et al*. 2004*b*). The central melanocortin system modulates energy homeostasis through the anorectic actions of the agonist α-melanocyte-stimulating hormone (a POMC cleavage product) and the endogenous orexigenic antagonist AgRP (Kalra *et al*.

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1999; Cone, 1999, 2005; Coll *et al.* 2004*b*). Five melanocortin receptors (MC*n*R, *n* 1–5) have been identified. The feeding-related effects of both α-melanocyte-stimulating hormone and AgRP are mediated via MC3R and MC4R. Both receptors are widely expressed in the hypothalamus and are found in the ARC, VMH and PVH (Kalra *et al.* 1999; Cone, 1999, 2005; Coll *et al.* 2004*b*).

Circulating hormones such as insulin (Kim *et al.* 1999), leptin (Ahima & Flier, 2000*b*), ghrelin (Nakazato *et al.* 2001; Cowley *et al.* 2003; Seoane *et al.* 2003), PYY (Batterham *et al.* 2002), glucocorticoids (Savontaus *et al.* 2002) and oestrogens (Fodor & Delemarre-van de Waal, 2001; Tritos *et al.* 2004) act on melanocortin AgRP and POMC neurons, providing information on energy status from the periphery. Hypothalamic POMC mRNA expression is regulated by nutritional status, with low levels during fasting that return to normal after leptin treatment or refeeding (Schwartz *et al.* 1997; Swart *et al.* 2002). In contrast, AgRP mRNA expression is increased by fasting, but unlike NPY mRNA levels, which are decreased after refeeding, AgRP levels remain elevated (Swart *et al.* 2002). Recent evidence also suggests that circulating macronutrients, such as glucose (Sergeyev *et al.* 2000; Fraley *et al.* 2002; Ibrahim *et al.* 2003) and lipids (Obici *et al.* 2002*b*; Morgan *et al.* 2004) modulate AgRP and POMC neurons.

The role of melanocortin signalling in body-weight homeostasis is fully supported by the phenotype of transgenic and knock-out mice, as well as identified human mutations. Transgenic mice over-expressing AgRP are obese (Ollmann *et al.* 1997) and reduction of hypothalamic AgRP by RNA interference reduces body weight (Makimura *et al.* 2002). However, AgRP-knock-out mice (as well as the double knock-out AgRP/NPY) show normal body weight and food intake (Qian *et al.* 2002), while selective ablation of AgRP/NPY neurons in adult mice results in hypophagia and leanness (Gropp *et al.* 2005; Luquet *et al.* 2005). The role of AgRP in human obesity is not well defined, but a polymorphism in the human *agrp* gene in man is associated with reduced body weight and fat mass (Marks *et al.* 2004). POMC-knock-out mice (Yaswen *et al.* 1999; Challis *et al.* 2004; Coll *et al.* 2005) and hucman (Krude *et al.* 1998) are hyperphagic and obese and display adrenal insufficiency. MC4R-knock-out mice (Huszar *et al.* 1997; Fan *et al.* 1997) and hucman (Yeo *et al.* 1998; Farooqi *et al.* 2000, 2003) also show hyperphagia and obesity. Finally, MC3R-knock-out mice display an increase in adiposity (Butler *et al.* 2000).

Melanin-concentrating hormone. MCH is an orexigenic neuropeptide expressed in the LHA–perifornical area. Central administration of MCH increases food intake and adiposity in rats and mice (Qu *et al.* 1996; Marsh *et al.* 2002). MCH receptor 1 antagonists inhibit food intake and induce weight loss (Borowsky *et al.* 2002). MCH expression is regulated by nutritional status; fasting induces MCH mRNA expression and leptin decreases it (Qu *et al.* 1996; Tritos *et al.* 2001).

The important role of MCH in appetite regulation is supported by the phenotype of GM models. Transgenic mice over-expressing MCH display hyperphagia and obesity (Ludwig *et al.* 2001; Marsh *et al.* 2002), while MCH-knock-out mice are hypophagic and lean (Shimada *et al.* 1998). Finally, the double knock-outs leptin/MCH have lower weight gain and adiposity compared with leptin-deficient *ob/ob* mice (Segal-Lieberman *et al.* 2003), suggesting that MCH is a downstream mediator of leptin effects on feeding. Finally, MCH receptor1-knock-out mice display a lean phenotype as a result of increased energy expenditure (Marsh *et al.* 2002).

Orexins. The OX (OX-A and OX-B), or hypocretins (hypocretins 1 and 2), are neuropeptides derived from the common precursor prepro-OX (also called prepro-hyprocretin) expressed in the LHA/perifornical area (de Lecea *et al.* 1998; Sakurai *et al.* 1998). Two different OX receptors have been cloned, termed OX 1 receptor (or hypocretin receptor 1) OX 2 receptor (or hypocretin receptor 2). Although OX expression in the brain is only located in the LHA–perifornical area (Broberger *et al.* 1998*a*; Elias *et al.* 1998*b*; Horvath *et al.* 1999), OX receptors show a widespread distribution in the CNS, with high levels of abundance in some hypothalamic nuclei (ARC, DMH, LHA, PVH and VMH; Marcus *et al.* 2001; Backberg *et al.* 2002). OX receptors are also present in the adrenal gland (López *et al.* 1999), pituitary (Blanco *et al.* 2001) gut (Kirchgessner & Liu, 1999), testis, kidney, ovary and placenta (Johren *et al.* 2001).

OX are important regulators of the sleep–wake cycle and the absence of OX signalling causes narcolepsy (Willie *et al.* 2001; Taheri *et al.* 2002; Sutcliffe & de Lecea, 2002). However, evidence also links OX to endocrine function (López *et al.* 1999, 2001*b*, 2004, 2005*b*; Barreiro *et al.* 2004; Seoane *et al.* 2004) and food intake regulation (Sakurai *et al.* 1998; López *et al.* 2001*a*, 2005*b*). Central administration of OX to rats stimulates feeding via a NPY-dependent mechanism (Sakurai *et al.* 1998; Dube *et al.* 2000; Ida *et al.* 2000; Jain *et al.* 2000; Yamanaka *et al.* 2000; López *et al.* 2002). Other evidence has linked the feeding actions of OX-A to opioids, corticotrophin-releasing hormone (Ida *et al.* 2000), urocortin and melanocortins (Wang & Kotz, 2002). Finally, prepro-OX-knock-out mice (Willie *et al.* 2001) and the OX/ataxin-3 transgenic mice in which OX-containing neurons are ablated (Hara *et al.* 2001) are hypophagic.

OX neurons are also responsive to peripheral signals regulating food intake. The expression of prepro-OX is increased in fasting and restored to normal by leptin (Sakurai *et al.* 1998; López *et al.* 2000; Zhu *et al.* 2002; Yamanaka *et al.* 2003). OX neurons in the lateral hypothalamus are also sensitive to glucose, being activated during hypoglycaemia (Cai *et al.* 1999; Griffond *et al.* 1999; Moriguchi *et al.* 1999). It has been also proposed that visceral feeding-related signals regulate OX actions, which are thought to act via the vagus nerve and the NTS. Thus, stimuli acting as 'terminate-eating' signals, such as gastric distension and glucose concentrations in the portal vein, appear to be important in the regulation of OX (Cai *et al.* 2001, 2002).

Despite evidence supporting the orexigenic effect of OX, it has been proposed (Hagan *et al.* 1999) that these effects are secondary, and are related to the state of arousal and vigilance necessary for normal feeding. However,

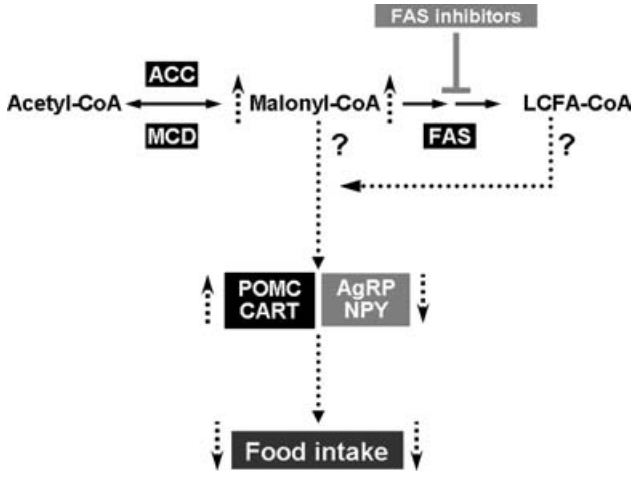

Fig. 2. Fatty acid synthesis pathway. Fatty acid synthesis is catalysed by acetyl-Co A carboxylase (ACC) and fatty acid synthase (FAS) in the cytoplasm. ACC catalyses the carboxylation of acetyl-CoA to malonyl-CoA. Acetyl-CoA and malonyl-CoA can be used as the substrates for the production of palmitate by the seven enzymic reactions catalysed by FAS. The synthesis step of malonyl-CoA is a reversible regulated mechanism, and malonyl-CoA decarboxylase (MCD) converts malonyl-CoA back to acetyl-CoA. The inhibition (⊥) of FAS (by using cerulenin, C75 or tamoxifen) increases the levels of malonyl-CoA in the hypothalamus, altering the concentration of long-chain fatty acid (LCFA)-CoA, which reduces feeding. The link between this effect and the neuropeptide changes is unknown (?). POMC, pro-opiomelanocortin; CART, cocaine- and amphetamine-regulated transcript; AgRP, agouti-related peptide; NPY, neuropeptide Y.

OX-A-induced feeding that is independent of arousal activation has been reported (Kotz *et al*. 2002).

Cocaine- and amphetamine-regulated transcript. CART is the third-most-abundant transcript in the hypothalamus and is expressed in the ARC, DMH, LHA and PVH (Kristensen *et al*. 1998; Elias *et al*. 2001; Hunter *et al*. 2004). Food deprivation decreases ARC expression of CART, while peripheral leptin treatment in *ob/ob* mice increases CART expression (Kristensen *et al*. 1998). Central administration of CART-(1–102) and CART-(82–103) inhibits feeding (Kristensen *et al*. 1998) and CART-knockout mice display a predisposition to become obese on a high-fat diet (Asnicar *et al*. 2001), an age-related increase in body weight and impaired glucose metabolism (Wierup *et al*. 2005), supporting the role of CART in the hypothalamic mechanism regulating food intake.

Lipid sensing in the hypothalamus

Although circulating lipids have for some time been hypothesised as signalling molecules that inform the hypothalamus of metabolic status, this function has only recently been definitively demonstrated. Following an elegant experimental approach Rossetti and colleagues (Obici *et al*. 2002*b*; Morgan *et al*. 2004) have shown that central administration of long-chain fatty acids such as oleic acid inhibits food intake via AgRP/NPY neurons in the ARC; this effect is not produced by medium-chain fatty acids. The physiological relevance of these data is intriguing. Since circulating NEFA can access the brain it is likely that the anorectic action of long-chain fatty acids may play an important role in the regulation of energy balance by acting as a 'nutrient abundance' signal (Lam *et al*. 2005*a*,*b*). Impairment of hypothalamic lipid-sensing in rats induces obesity (He *et al*. 2006), as well alterations in plasma glucose (Pocai *et al*. 2006), indicating that this mechanism may be important in the physiological regulation of metabolism and body-weight homeostasis.

Fatty acid synthesis pathway in the hypothalamus

Recent reports demonstrate that the enzymes of the fatty acid synthesis pathway (Fig. 2) are expressed in the hypothalamus. Acetyl-CoA carboxylase, FAS and malonyl-CoA decarboxylase mRNA and proteins have been detected in the ARC, DMH, PVH and VMH (Kim *et al*. 2002; López *et al*. 2006). The anatomical location of these enzymes suggests that they may play a role in the hypothalamic mechanism regulating feeding. This notion is further supported by evidence demonstrating that peripheral and central administration of the FAS inhibitors cerulenin, C75 and tamoxifen reduces food intake and body weight through a malonyl-CoA-dependent mechanism (Loftus *et al*. 2000; Hu *et al*. 2003; Lelliott *et al*. 2005; López *et al*. 2006). The anorectic action of FAS inhibitors is linked to decreased expression of AgRP/NPY and elevated expression of CART/POMC in the neurons of the ARC, although the molecular mechanisms of this interaction have not yet been completely defined (Loftus *et al*. 2000; Shimokawa *et al*. 2002; López *et al*. 2006). Additionally, it has been demonstrated that nutritional status regulates hypothalamic malonyl-CoA levels and FAS expression in a nucleus-specific manner, with FAS mRNA levels down regulated by fasting and up regulated by refeeding, an effect specific to the VMH (Fig. 3; López *et al*. 2006). This evidence suggests that the regulation of FAS could be a physiological mechanism of food-intake control and that the increase in malonyl-CoA induced by FAS inhibition may act as central lipid-sensing signal.

Brainstem regulation of food intake

The brainstem plays an essential role in the regulation of body-weight homeostasis. The NTS is anatomically close to the area postrema, a circumventricular organ, like the ARC, with a partial BBB (Stanley *et al*. 2005). Consequently, the NTS is in a perfect location to receive peripheral circulating signals, as well as vagal afferents from the gastrointestinal tract and the glossopharyngeal nerves (Kalia & Sullivan, 1982; Sawchenko, 1983).

The NTS contains GLP-1, NPY and melanocortin neuronal circuits. GLP-1-expressing neurons comprise the main brainstem circuit modulating feeding. In the CNS GLP-1 is only synthesised in the caudal NTS. GLP-1 fibres project to the PVH and DMH, with fewer projections to the ARC (Stanley *et al*. 2005). Central administration of GLP-1 into either the third ventricle or the fourth ventricle reduces food intake, and treatment with the GLP-1 receptor

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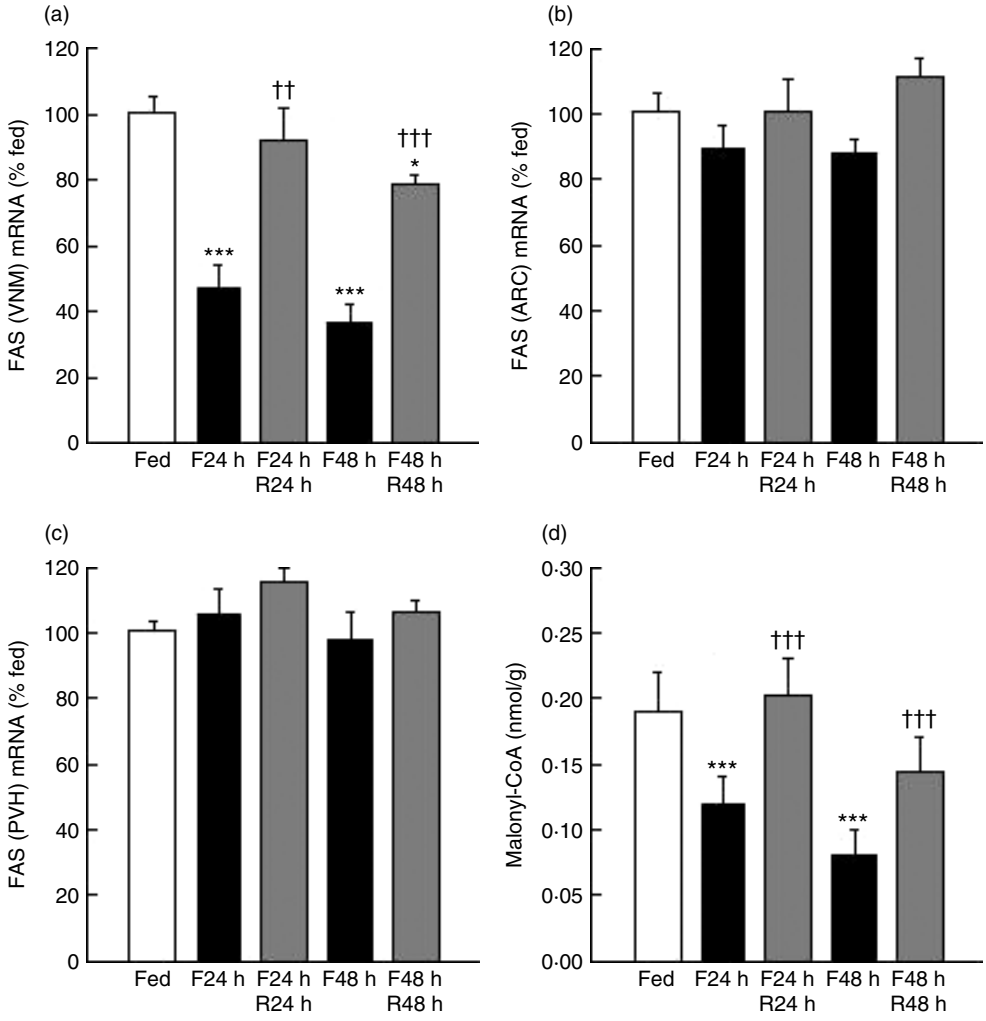

Fig. 3. Fatty acid synthase (FAS) expression and malonyl-CoA levels are nutritionally regulated in the rat hypothalamus. Expression of FAS in the ventromedial nucleus of the hypothalamus (VMH; a), arcuate nucleus (ARC; b) and paraventricular nucleus (PVH; c), and malonyl-CoA levels (d) of fed rats (□), fasted (F; ■) rats and F + refed (R; ▩) rats. Values are means with their standard errors represented by vertical bars. Mean values were significantly different from those for fed rats: *$P<0·05$, ***$P<0·001$. Mean values were significantly different from those for the corresponding F rats: ††$P<0·01$, †††$P<0·001$.

antagonist exendin (9-39) increases appetite (Turton *et al*. 1996). This finding suggests a role for endogenous GLP-1 in energy homeostasis. NPY neurons from the brainstem project to the PVH (Sawchenko *et al*. 1985), and extracellular NPY levels within the NTS are nutritionally-regulated (Yoshihara *et al*. 1996). Y_1 and Y_5 receptors are also located in the NTS (Harfstrand *et al*. 1986; Dumont *et al*. 1998; Glass *et al*. 2002). POMC-derived peptides are synthesised in the NTS of the rat (Kawai *et al*. 1984; Bronstein *et al*. 1992; Fodor *et al*. 1996). Brainstem POMC neurons are activated by feeding and also by CCK treatment (Fan *et al*. 1997). MC4R are also expressed in the NTS (Mountjoy *et al*. 1994) and act to modulate energy intake. Fourth-ventricle administration of a MC3R/MC4R agonist decreases food intake, and MC3R/MC4R-antagonist administration to these areas increases food intake (Williams DL *et al*. 2000).

Prolactin-releasing peptide is expressed in the NTS, in addition to the hypothalamic DMH (Lee *et al*. 2000). Prolactin-releasing peptide expression is reduced in fasting, and central administration of prolactin-releasing peptide decreases appetite by a corticotrophin-releasing hormone- and CCK-mediated mechanism (Seal *et al*. 2001; Ellacott *et al*. 2002; Lawrence *et al*. 2004). Chronic administration of prolactin-releasing peptide does not affect food intake (Ellacott *et al*. 2003), suggesting a role in short-term appetite regulation instead of long-term control of body weight.

Reward and regulation of food intake

Even in the absence of an energy deficit, the rewarding nature of food may act as a stimulus to feeding. Several signals are able to modulate reward pathways.

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The reward circuitry is complex, involving interactions between several signalling systems, including the opioid, dopaminergic and endocannabinoid (EC) systems (Cota *et al*. 2003*a*,*b*; Flier, 2004; Di Marzo & Matias, 2005; Lichtman & Cravatt, 2005; Fulton *et al*. 2006; Hommel *et al*. 2006).

Opioids. Opioids play an important role in the regulation of feeding. The anatomical site for opioid action is the nucleus accumbens (Zhang & Kelley 2000; Zhang *et al*. 2003). Mice lacking enkephalin or β-endorphin lose the reinforcing property of food, despite the palatability. This effect is overridden after fasting, indicating that homeostatic mechanisms can overrule the hedonistic pathway (Hayward *et al*. 2002). In man opiate antagonists decrease food palatability without altering subjective hunger (Yeomans *et al*. 1990; Drewnowski *et al*. 1992).

Endocannabinoids. The effect of marijuana (*Cannabis sativa*) to increase appetite has been known for many years (Di Marzo & Matias, 2005; Lichtman & Cravatt, 2005). The primary constituent of cannabis is Δ^9tetrahydrocannabinol; this molecule, along with other naturally-occurring and synthetic cannabinoids (CB), binds to two separate G-protein-coupled receptors: the CB1 receptor, which is located in the CNS and periphery; the CB2 receptor, which is primarily found in cells of the immune system (Matsuda *et al*. 1990; Devane *et al*. 1992; Munro *et al*. 1993). These receptors also bind endogenous ligands, the EC, which include the fatty acid amide N-arachidonoyl ethanolamine (anandamide) and the monoacylglycerol 2-arachidonoylglycerol (Di Marzo *et al*. 2001; Cota *et al*. 2003*a*; Di Marzo & Matias, 2005; Lichtman & Cravatt, 2005).

Central and peripheral administration of EC stimulates food intake (Williams *et al*. 1998; Koch, 2001; Cota *et al*. 2003*a*). This orexigenic effect is mediated via CB1 receptors in the hypothalamus, which co-localise with CART, corticotrophin-releasing hormone, MCH and OX (Cota *et al*. 2003*b*). Additionally, CB1-knock-out mice display hypophagia and leanness (Cota *et al*. 2003*b*), and leptin-deficient signalling is associated with high hypothalamic EC levels (Di Marzo *et al*. 2001). Recent evidence (Verty *et al*. 2004) has also shown that the EC receptors are located downstream from the melanocortin system.

Together this evidence supports the important role of the EC system in the regulation of feeding. In fact, there is currently a CB1 selective antagonist, Rimonabant (SR141716), in use in phase III clinical trials that may be a potentially promising anti-obesity drug (Di Marzo & Matias, 2005).

Dopamine. The dopaminergic system is also important in the rewarding circuitry of feeding regulation (Fulton *et al*. 2006; Hommel *et al*. 2006). In fact, mice lacking tyrosine hydroxylase, the enzyme synthesising dopamine, are hypophagic (Szczypka *et al*. 2001). These actions are mediated via D_1 and D_2 receptors (Szczypka *et al*. 2001).

Serotonin. Serotonin plays an important role in regulating both rewarding and homeostatic mechanisms (Halford & Blundell, 2000*b*). Serotonin actions of food intake are mediated via the melanocortin system (Heisler *et al*. 2002, 2003). In fact, the currently-discontinued anorectic agent fenfluramine mediates its actions via serotonin and melanocortins (Heisler *et al*. 2002).

Conclusions

Multiple, redundant and complex peripheral neural circuits participate in the regulation of food intake and body-weight homeostasis. All this evidence indicates that obesity, and associated metabolic alterations, is complex, multifactorial and chronic pathology. Thus, the search for, and development of, new weight-loss drugs is made extremely complicated. In fact, the efficacy of drugs acting on a single molecular target might be limited by compensatory feedback mechanism. In the near future combined therapies that act on both peripheral and central targets should be sought. Understanding these molecular networks regulating food intake could lead to the design of better therapeutic targets for weight loss.

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