Introduction

Obesity is a serious medical condition whose prevalence is rising. Figures from the Health Survey for England show that, in 1980, 8% of women and 6% of men were classified as obese, as defined by a body mass index (BMI) of greater than 30 kg/m². By 2001, these proportions had increased to 26% and 22%, respectively, with 55% of women and 66% of men being overweight (BMI > 25 kg/m²; Health Survey for England, 2001), reflecting a worldwide trend which is most marked in, but not restricted to, the developed world. Most of us in affluent countries live in a privileged land of plenty where high calorie foods are easily available and in which we have a limited need for exercise. The rising prevalence of obesity in children is of particular concern (Chinn & Rona, 2001).

Obesity is associated with significant morbidity and mortality, which can be attributed to increased risk of a number of medical conditions (Kopelman, 2000) including type II diabetes mellitus, hypertension and coronary heart disease, the most common cause of premature mortality in the obese population. Less well known are the associations between obesity and several cancers including breast, endometrial, prostate and bowel cancer (Daling et al., 1996). Chronic administration of insulin to rodents, either into the third ventricle or directly into the hypothalamus, causes a reduction in food intake (Baura et al., 1993). However, patients with type II diabetes who are commenced on insulin tend to gain rather than lose weight, probably as a result of a loss of the anorexigenic effect of hyperglycaemia and the lipogenic actions of insulin.

Peripheral hormones regulating appetite

Insulin

Almost 50 years ago, Kennedy (1953) postulated that there was a circulating factor, related to or arising from adipose tissue, that regulated the hypothalamic control of food intake to achieve the usual long-term stability of body weight and fat mass. Insulin was the first hormone postulated to be such a factor. The rise in circulating insulin in response to a glucose load is proportional to fat mass, and insulin reaches the CNS via receptor-mediated transport across the blood–brain barrier. CNS administration of insulin to rodents, either into the third ventricle or directly into the hypothalamus, causes a reduction in food intake (Baura et al., 1993). However, patients with type II diabetes who are commenced on insulin tend to gain rather than lose weight, probably as a result of a loss of the anorexigenic effect of hyperglycaemia and the lipogenic actions of insulin.

Leptin

In 1994 there was a major breakthrough when the obese (ob) gene was identified from examination of naturally occurring mutant ob/ob mice (Zhang et al., 1994). The protein encoded by the ob gene was named leptin from the Greek leptos meaning thin, synthesized predominantly in adipose tissue. Circulating leptin levels are directly proportional to adiposity in animals and humans and correlate better with total fat mass than with body weight (Considine et al., 1996). Central and peripheral administration of leptin in rodents cause a profound decrease in food intake and weight loss (Friedman & Halaas, 1998). However it is the central intracerebroventricular (ICV) route that is the more potent, suggesting that leptin’s actions are mediated chiefly through the hypothalamus. The ob/ob mouse, completely deficient in leptin, is hyperphagic, hyperinsulinaemic and very obese and the leptin receptor defective db/db mouse has a similar phenotype (Chua et al., 1996). Chronic administration of leptin to the ob/ob mouse results in sustained reduction in body weight, and reduced food intake but has no effect on the db/db mouse.

Leptin increases hours after a meal in rodents and after several days of overeating in humans (Kolaczynski et al., 1996).
Conversely, leptin levels fall dramatically with fasting. The magnitude of these responses is disproportionate to changes in fat mass, suggesting that leptin may act to stabilize body weight before a major change in weight occurs. In starvation, in which leptin levels are further reduced, there is activation of the hypothalamo–pituitary axis (HPA) and suppression of reproduction, the thyroid axis and the immune system (Ahima et al., 1996; Lord et al., 1998). When leptin is administered in the fasting state, these effects are blunted. Thus leptin plays a key role in signalling and survival in times of food deprivation as well as in food excess. The importance of the leptin pathways in the control of human body weight has been demonstrated by the childhood-onset obesity and hyperphagia associated with rare congenital leptin deficiency in humans. Treatment of three leptin-deficient children with recombinant leptin has led to a significant reduction in hyperphagia and fat mass (Farooqi et al., 2002). However, the vast majority of obese people have high circulating leptin concentrations due to normal ob genes and reflecting their high fat mass (Considine et al., 1996). Leptin treatment appears to be safe and well-tolerated, but has been of limited benefit in treating obesity in nonleptin-deficient people (Mantzoros & Flier, 2000). It remains to be seen whether leptin may be better at maintaining rather than inducing weight loss.

**Gastrointestinal peptides**

**Ghrelin**

In 1999 ghrelin was identified as the endogenous ligand for the growth hormone secretagogue receptor (GHS-R). It is a small 28 amino acid peptide with an acyl side chain which is essential for its biological action (Kojima et al., 1999). Interestingly, ghrelin is synthesized predominantly in the stomach. In addition to stimulating GH, ghrelin has been shown to increase food intake when administered both peripherally and centrally (Wren et al., 2000). Although there are many peptides that have orexigenic actions when administered centrally, ghrelin is the only peptide hormone found to stimulate appetite when administered peripherally.

Ghrelin is thought to signal premeal hunger and meal initiation. Endogenous levels of ghrelin in man rise on fasting and fall rapidly on re-feeding with sharp peaks occurring just before each meal (Cummings et al., 2001). Ghrelin also appears to play a role in longer-term appetite regulation and energy balance. Chronic administration of ghrelin in rodents leads to continuing hyperphagia and weight gain independent of GH secretion (Tschop et al., 2000). Circulating ghrelin decreases in response to chronic overfeeding and increases in response to chronic negative energy balance associated with exercise or anorexia nervosa. Whereas obese people usually have high plasma leptin they have low plasma ghrelin (Tschop et al., 2001).

Intravenous ghrelin is effective in stimulating food intake in humans. A recent study has shown a 28% increase in food intake from a free buffet meal in healthy volunteers with a ghrelin infusion compared with saline control (Wren et al., 2001). Additionally, there were increases in subjective hunger as measured by visual analogue scales. Ghrelin or a synthetic analogue could be a possible therapy to increase food intake in cachexia and anorexia. Conversely, an antagonist at the ghrelin GHS-R receptor could be an obesity treatment. The challenge in any antiobesity
drug is to find an agent that reduces appetite and food intake without affecting other endocrine systems. In the case of ghrelin, one would want to block the feeding effects at the GHS-R without significantly reducing circulating GH. Circulating ghrelin achieves its orexigenic action through stimulation of hypothalamic neurones (Nakazato et al., 2001), and inhibitory actions on the gastric vagal afferent nerve (Date et al., 2002).

Peptide YY

Peptide YY (PYY) is secreted from the endocrine L cells of the small and large bowel, and released into the circulation after meals. PYY is a member of the neuropeptide Y (NPY) family with a tyrosine residue at both ends. The main form of PYY in both the gut mucosal endocrine cells and the circulation, is PYY 3–36 (Grandt et al., 1994). Peripheral administration of PYY 3–36 leads to a marked inhibition in food intake. In human volunteers, an exogenous infusion accurately mimicking postprandial PYY 3–36 concentrations reduced food intake by 30% when compared with saline control in a double-blinded cross-over study with no adverse effects (Batterham et al., 2002). PYY3-36 has a high affinity for the Y2 receptor (Y2R), a member of the NPY receptor family. The pattern of c-fos neuronal activation following peripheral administration of PYY 3–36 suggests that its action is via the hypothalamus, where the Y2 is located.

In contrast with the negligible effect on appetite caused by the normal daily fluctuations in circulating leptin (Sinha et al., 1996), PYY 3–36 inhibits food intake in rodents and man at physiological concentrations. Thus PYY 3–36 is likely to be important in the everyday regulation of food intake. Further work is needed to determine whether PYY 3–36 is effective in obese people, and whether the Y2 receptor could be a future drug target.

Glucagon-like-peptide-1

Glucagon-like-peptide 1 (GLP-1) is co-secreted with PYY in response to nutrients in the gut. The precursor prepro-glucagon is cleaved tissue-specifically – in the pancreas it forms glucagon whereas in the intestinal L cells it gives rise to GLP-1. Central ICV injection of GLP-1 powerfully inhibits feeding in rodents (Turton et al., 1996).

GLP-1 plays an additional role in enhancing insulin secretion and suppressing glucagon secretion after a meal, functioning as an incretin (Kreymann et al., 1987). The plasma insulin response to a given rise in plasma glucose is much greater after an oral glucose load than after an intravenous glucose infusion and this difference can be attributed to the rise in circulating GLP-1 and gastric inhibitory polypeptide (GIP) Stimulated by the oral glucose.

GLP-1 is the most powerful incretin known in man. Infusion of GLP-1 to healthy volunteers increases plasma insulin levels and inhibits glucagon release (Kreymann et al. 1987). Human data on whether GLP-1 inhibits feeding in humans is conflicting. A recent meta-analysis shows that GLP-1 causes a small dose-dependent inhibition of food intake in both lean and overweight subjects (Verdich et al., 2001). Reduction in the rate of gastric emptying may contribute to the increased satiety induced by GLP-1.

The combination of enhanced insulin release with probable reduction of food intake makes GLP-1 an attractive treatment for patients with type II diabetes. A 6-week trial of three subcutaneous GLP-1 premeal injections per day improved glycaemic control by increasing insulin levels and inhibiting glucagon compared with placebo control with no adverse effects (Todd et al., 1997). Exendin-4, the GLP-1 receptor agonist with a longer biological action than GLP-1, is currently undergoing phase III clinical trials (Egan et al., 2002). An alternative therapeutic strategy is to target the enzymes such as dipeptidyl peptidase-4 (DPP4), which catalyse the breakdown of GLP-1. After 4 weeks of three subcutaneous premeal injections of the DPP4 inhibitor NVP DPP728, there was an improvement in glycaemic control compared with placebo, but without the additional benefit of weight loss (Ahren et al., 2002).

Cholecystokinin

Cholecystokinin (CCK) was the first gut hormone shown to inhibit feeding following exogenous administration in rodents (Gibbs et al., 1973). CCK_ receptors, present on the vagus nerve and pyloric sphincter, are bound exclusively by the sulphated forms of CCK and are active in reducing food intake (Moran, 2000). Other well-known functions of CCK include the stimulation of pancreatic enzyme secretion and gallbladder contraction – effects mediated via both CCK_ and CCK_ receptors.

Peripheral CCK has a rapid but relatively short-lived effect on feeding, exerting its maximum inhibition within 30 min post-injection (Moran, 2000) which is consistent with a role in mediating satiety and meal termination. High-dose CCK may also cause nausea, vomiting and taste aversion, although lower doses have been shown to inhibit feeding without inducing these effects (West et al., 1987). However, tolerance is exhibited with prolonged CCK administration after 24 h (Crawley & Beinfeld, 1983). Although meal size was persistently reduced with the CCK infusion, there was compensatory increase in meal number. There is, however, evidence that CCK may play a role in longer-term energy regulation by synergizing the actions of leptin. Central leptin administration potentiates the feeding inhibition of peripheral CCK and the CCK/leptin combination results in greater weight loss over 24 h than does leptin alone (Matson et al., 1997). This synergy may occur by CCK activating brain stem neurones that project to the hypothalamus combined with leptin’s direct hypothalamic actions.
Central appetite regulation

The hypothalamus

The hypothalamus can be subdivided into nuclei consisting of collections of neurones with discrete functions (Fig. 2). Neuronal projections between these nuclei and to and from other areas in the brain enable the hypothalamus to integrate signals from the brain, the peripheral circulation and the gastrointestinal tract to regulate energy intake and expenditure.

The arcuate nucleus (ARC), termed infundibular nucleus in man, is situated at the base of the hypothalamus. This is an elongated arc-shaped collection of neuronal cell bodies which express receptors for many of the hormones and neuropeptides that are known to regulate feeding. The arcuate nucleus is a privileged site which can sample the peripheral circulation through semi-permeable capillaries in the underlying median eminence, and is thus in an ideal position to integrate hormonal signals for energy homeostasis. The paraventricular nucleus (PVN) is adjacent to the superior part of the third ventricle in the anterior hypothalamus. The PVN is the main site of corticotrophin-releasing hormone (CRH) and TRH secretion, in addition to being richly supplied with neuronal projections from the ARC. Thus the PVN plays a role in the integration of nutritional signals with the thyroid and HPA axes.

The brain stem

One of the satiety signals following a meal is from afferent fibres of the vagus nerve to the brain stem (Williams et al., 2001). The hypothalamus and brain stem are linked via projections from NTS neurones to the PVN and lateral hypothalamus, such as GLP-1 neurones, and projections of serotoninergic neurones of the Raphe nuclei to the arcuate nucleus. The role of the brain stem in appetite and feeding regulation has been examined using experimental decerebrate rats in which connections between the brain stem and forebrain are severed surgically (Grill & Smith, 1988). The decerebrate rats were able to compensate for changes in the composition of individual meals offered to them. However, when challenged with a reduction in meal number from three to two per day, intact rats compensated by increasing their food intake at each meal, but the decerebrate rats failed to adjust their meal size. Thus while the brain stem plays a role in individual meal size, the hypothalamus is required for long-term energy balance and appetite regulation.

Orexigenic hypothalamic neuropeptides

NPY and Agouti-related protein (AgRP)

NPY is a 36 amino acid neuropeptide which is one of the most potent orexigenic agents known. A single ICV injection acutely stimulates feeding in rodents. Chronic administration of NPY into the hypothalamic PVN leads to sustained hyperphagia and weight gain, and central injection of NPY antagonists or antisemum decreases food intake in the dark phase when rats normally eat readily (Kalra et al., 1999). There is a rapid increase in NPY before mealtimes in the PVN, and levels remain elevated as long as food is withheld, suggesting that NPY plays a role in the central control of meal initiation. NPY acts to stimulate feeding predominantly through activation of Y1 and Y5 receptors. NPY also has multiple actions on the HPA, on seizure activity and on responses to stress and anxiety, which may limit its use as a drug target for obesity.

AgRP increases food intake through antagonism of the melanocortin MC3 and MC4 receptors and thus blockade of the inhibition of the anorexigenic agonist α-melanocyte-stimulating hormone (α-MSH; see below). In contrast to the potent but relatively short-lived effects of NPY, central administration of AgRP to rodents leads to an increase in food intake for up to 1 week (Rossi et al., 1998). Chronic administration of AgRP to rodents causes sustained hyperphagia and leads to obesity (Small et al., 2001). AgRP is found exclusively in the arcuate nucleus, and virtually all AgRP neurones co-secrete NPY (Goldstone et al., 2002).

NPY/AgRP neurones are inhibited by leptin and insulin, and activated by ghrelin (Kalra et al., 1999; Nakazato et al., 2001). The Y2R is a presynaptic inhibitory autoreceptor on NPY neurones. Injection of PYY3-36, the gut-derived Y2R agonist, directly into the ARC inhibits food intake. The appetite inhibitory effects of PYY3-36 are absent in the Y2 knockout mouse (Batterham et al., 2002). Therefore it appears that circulating PYY3-36 inhibits appetite by acting directly on the arcuate

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nucleus to inhibit orexigenic NPY neurones. Thus low circulating leptin, insulin and PYY3-36, and elevated ghrelin levels such as in fasting or starvation lead to an increase in NPY and AgRP neuronal activity and increased appetite, whereas the opposite is seen postprandially (Fig. 1).

**Anorectic hypothalamic neuropeptides**

**The melanocortins**

The melanocortins are derived from the precursor molecule pro-opiomelanocortin (POMC) via tissue-specific post-translational cleavage. In the anterior pituitary, POMC gives rise to ACTH, which acts via the MC2 receptor to stimulate adrenal steroidogenesis. The melanocortin α-MSH is derived from POMC in brain. The MC3 and MC4 receptors are biologically unique in that there is an endogenous antagonist (AgRP) in addition to endogenous agonists (the melanocortins).

Central ICV administration of α-MSH inhibits feeding and reduces body weight. The stimulatory effect of AgRP is inhibited by α-MSH (Rossi et al., 1998). Thus α-MSH and AgRP neurones act as a dynamic system in vivo.

POMC is co-expressed in arcuate neurones with cocaine- and amphetamine-regulated transcript (CART), and these neurones are directly stimulated by leptin (Cowley et al., 2001). Peripheral administration of PYY 3–36 increases POMC expression and inhibits NPY expression (Batterham et al., 2002). These changes in message levels may explain the long duration of action of PYY.

The MC4 receptor, in particular, is thought to be critical to body weight regulation. The MC4 knockout mouse is hyperphagic and very obese, and insensitive to α-MSH (Huszar et al., 1997). Functional mutations of the MC4 receptor are also a cause of monogenic human obesity and are much more common than leptin deficiency, being found in up to 4% of adults with severe childhood-onset obesity (Farooqi et al., 2000). The minority with homozygous mutations tend to be more severely obese. For the majority of obese patients who have intact melanocortin receptors, agonists at these receptors and, in particular, the MC4 receptor could reduce appetite and food intake. The prolonged action of the endogenous antagonist AgRP suggests that manipulation of the melanocortin system could have long-lasting effects. Melanocortin receptor agonists are currently being developed as potential obesity treatments. Recently it was demonstrated that intranasal administration of a fragment of melanocortin (MSH/ACTH1-10), common to all melanocortins, leads to modest weight reduction in humans (Fehm et al., 2001).

**Serotonin**

Serotonin (5-HT) is a short-acting widespread neurotransmitter which acts on a number of receptor subtypes found at high density in the limbic system and Raphe nuclei as well as in the hypothalamus (Blundell, 1984). In general, agonists at the 5-HT receptors and drugs that inhibit the re-uptake of serotonin reduce feeding. Additionally, 5-HT stimulates noradrenaline release and modifies behaviour and mood.

Agonists at the 5-HT_{2C} receptor show the most consistent inhibition of food intake, and the 5-HT_{2C} knockout mouse is hyperphagic and obese (Tecott et al., 1995). Additionally, this knockout mouse has a low seizure threshold and exhibits severe and life-threatening epilepsy. However, 5-HT_{2C} antagonists do not cause hyperphagia or epilepsy. This apparent dichotomy could be explained if the phenotype of the knockout mouse had been altered through adaptation, and illustrates the potential limitations in the extrapolation of the function of a neuropeptide from its knockout model.

**Current treatments for obesity**

The first-line treatment for obesity is food restriction and exercise. However, most people find it difficult to lose weight despite a wide choice of diets and exercise programmes, and even more difficult to maintain weight loss (Yanovski & Yanovski, 2002). Current second-line treatments are the medications sibutramine and orlistat, and surgery.

**Pharmacological therapy**

Sibutramine, a serotonin and noradrenaline re-uptake inhibitor, is recommended by the National Institute of Clinical Excellence (NICE) for the treatment of obesity in patients with a BMI of over 30 kg/m^2 or the presence of an obesity-related disease and a BMI of over 27 kg/m^2 (NICE, 2001). The earlier drugs fenfluramine and dexfenfluramine, which acted through stimulation of 5-HT secretion as well as inhibition of 5-HT re-uptake, were withdrawn following the discovery of an association with their use and cardiac valve abnormalities (Connolly et al., 1997). In a recent European trial (James et al., 2000), following a 6-month run-in period on sibutramine, patients who achieved a 5% reduction in weight were randomized to either continue with sibutramine or receive placebo. At 18 months, 69% of patients on sibutramine compared with 42% of controls retained this modest 5% reduction. Sibutramine may cause an increase in blood pressure and pulse (acting as a sympathomimetic) and is therefore unsuitable for hypertensive patients. In normotensive patients, treatment with sibutramine may achieve moderate weight loss for a limited period at least.

Orlistat acts locally in the gut by binding to gastrointestinal lipases to inhibit fat absorption. Patients who take orlistat with or 1 h after meals excrete approximately one-third of their ingested dietary fat in their stools, thereby reducing calorie intake. Consequently, they may have flatulence and offensive
stools after a fatty meal. Trials show that orlistat can also achieve mild weight loss of 9% at 1 years compared with 5% of placebo and may slow the regain of weight for a second year of use (Yanovski & Yanovski, 2002). However, orlistat is only licensed for 2 years, and is less effective by the second year.

**Surgery**

Surgery is the only treatment which has been proven to achieve weight loss in the long term. The jejunoo-intestinal bypass has been performed since the 1960s and leads to impressive weight loss up to 15 years (Frandsen et al., 1998). However, its use has been limited by serious complications including liver failure, severe electrolyte imbalance, renal calculi due to impaired oxalate absorption, osteomalacia and bypass enteritis.

The Roux-en-Y gastric bypass has now been largely superseded the jejunoo-intestinal bypass. This technique involves cutting the jejunum, and joining the distal end to the body of the stomach (the Roux-en-Y) and the proximal part to another part of jejunum distal to the Roux-en-Y. The stomach is stapled, leaving a 10–15 ml fundal pouch which drains directly into the jejunum. The advantages of the gastric bypass over the jejunoo-intestinal bypass are that there is no blind loop, the bile can drain through the duodenum and into the jejunum and there is less severe malabsorption. In one series, mean weight loss at 15 years postgastric bypass surgery was 30 kg (Mitchell et al., 2001) compared with 43 kg in another study following jejunoo-intestinal surgery (Frandsen et al. 1998) but with the benefit of fewer complications. Nonetheless, the morbidity associated with gastric bypass surgery, in addition to practical and financial constraints, usually limit this approach to severely obese patient (BMI > 40 kg/m²).

Interestingly, the success of bypass surgery may be as much hormonal as mechanical. Fasted rats with jejunoo-intestinal bypass ate 32% less in the first hour of re-feeding than fasted rats given a sham procedure (Atkinson & Brent, 1982). When plasma from the bypass group following feeding was injected into a new group of fasting rats, the recipients ate 32% less in the first hour than rats injected from plasma from the sham bypass group. Thus it appeared that the reduction in appetite was hormonally driven. After intestinal resection in the rat, there is significant elevation in the concentration of PYY (Savage et al., 1985). With our current knowledge of the PYY 3–36 circuity from the gut to the ARC of the hypothalamus, it is tempting to hypothesize that elevated circulating PYY 3–36 levels in patients with gastric or intestinal bypass contribute to a reduction in appetite and food intake. Gastric bypass surgery may also affect circulating ghrelin. Plasma ghrelin concentrations were recently measured in obese patients before and after diet-induced weight loss, and in patients who had previously undergone gastric bypass surgery. As predicted, circulating ghrelin increased with diet-induced weight loss. However, ghrelin levels were 77% lower in the gastric bypass group compared with matched BMI controls, and the usual premeal peaks were lost (Cummings et al., 2002). Under normal circumstances the presence of nutrients in the stomach is believed to suppress ghrelin secretion from the stomach. However, the observations of this study suggest that prolonged absence of nutrients or surgical manipulation of the stomach suppresses ghrelin secretion. Reduced circulating ghrelin with a possible elevation of circulating PYY 3–36 could account for the paradoxical decrease in hunger reported by most patients, and explain the long-term weight loss usually seen following gastric bypass surgery.

**Conclusion**

The current epidemic of obesity is threatening the health of the western world. We have explored how appetite is regulated by the circulating hormones leptin and insulin, and the gut hormones ghrelin and PYY 3–36, and signalled to the hypothalamus. Exciting potential pharmacological targets include the receptors of orexigenic ghrelin and anorexigenic PYY 3–36. Further understanding is required to enable us to develop more effective treatments, not only to inhibit appetite in the obese but also to stimulate appetite in cachectic patients. While many of the signals and circuits described in this article might be manipulated, the real challenge is to find treatments that modify appetite and lead to lasting weight reduction selectively without significantly affecting other neuroendocrine systems.

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**References**


