Drug treatment of obesity: from past failures to future successes?

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Keywords: glucagon-like peptide-1, human, leptin, melanocortin-4 receptor, neuropeptide Y, obesity, orexins, orlistat, sibutramine, thermogenic agents, uncoupling proteins

Introduction

Obesity is one of the last great unfilled niches in pharmacotherapy. In many ways, this is a curious gap, because obesity is such a common, serious and costly disorder. Obesity of a clinically significant degree is now twice as common in the UK as it was 12 years ago, with one adult in six having a body-mass index (BMI) of over 30 kg m^{-2} [1] – the threshold for sharp increases in the development of obesity-related diseases such as type 2 diabetes, hypertension and atheroma. These diseases and many other problems, ranging from osteoarthritis of the hips and sleep apnoea to depression and damaged employment prospects, can impose considerable physical and mental burden on the obese individual. Ultimately, obesity absorbs a substantial share (probably 5–8%) of total health-care expenditure in most Westernized countries [2]. Developing countries, in which the obesity epidemic has already been unleashed by the advent of westernization ('Cocacolonization'), will find it particularly difficult to cope with the impact of this expensive disorder.

Until recently, several factors have militated against active investment in antiobesity drug development. These include indifference and ignorance by the medical profession (most of whom have received little or no instruction about obesity), the poor safety and efficacy track-records of previous antiobesity drugs, and the lack of compelling targets for drug discovery. Now, all major pharmaceutical companies have active programmes in obesity; indeed, researchers in the industrial sector have contributed some of the most exciting recent advances in the understanding the molecular biology of normal energy homeostasis and obesity. The climate has changed mainly because the application of advanced molecular methods to this previously unfashionable area has answered some old

conundrums and produced some promising drug targets. At the same time, the medical profession and even some governments have at last begun to grasp the gravity of this issue. The size of the global market, perhaps £200 billion per year, may also have tempted some companies to invest the 10–12 years and £0.3 billion that are generally needed to bring a new drug to market.

In this review, we shall first deal with aspects of the pathogenesis of obesity and then discuss current and some future prospects of drug therapy in this disease.

Energy balance and obesity

Regulation of body fat and weight

Under relatively steady-state conditions, body weight in adults is maintained to within 1% over periods of days to weeks. The homeostatic circuits involved are multiple, complex and still poorly understood. From first principles, there should be both short-term controls, to initiate and terminate each meal, and longer-term regulation to keep body energy reserves (mainly triglyceride stored in fat tissue) at an appropriate and constant level. Short-term signals may include a small fall in the plasma glucose level ($<1 \text{ mmol l}^{-1}$), which is thought to trigger spontaneous feeding episodes in rodents and perhaps in man, and various satiety signals to indicate when enough has been eaten. The latter probably include various gut peptides (e.g. cholecystokinin) released after food enters the gut, as well as distension of the stomach and a rise in glucose in the portal vein, both of which are sensed by vagal receptors and conveyed by the vagus to the nucleus of the solitary tract in the medulla and thence to the hypothalamus. The longer-term regulation of energy stores demands other signals that indicate fat mass and that can be received and integrated by the brain so as to adjust food intake and energy expenditure appropriately. Signals proven to have such a role include, at least in rodents, the hormones leptin and insulin.

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Received 27 March 2000, accepted 22 August 2000.

Pathogenesis of obesity

Fundamentally, the development of obesity is one of the least mysterious processes in human disease: in energetic terms, it arises simply from an excess of energy intake over energy expenditure. The imbalance need not be great: 1 kg of fat contains about 7000 cal, so the 10 kg commonly gained during the fourth decade could be explained by an excess of only 20–30 cal per day – a few grams of chocolate or 20 min watching television instead of walking the dog.

Decreased energy expenditure is as important as increased energy intake in causing obesity, indeed, probably more so in the current obesity epidemic that is cutting through the Westernized world. Over the last 10–20 years of rapidly increasing obesity in the UK, the population's energy intake has remained roughly constant, but levels of physical activity have steadily declined [3]: overall therefore obesity has developed because we have failed to reduce our energy intake to match our falling energy expenditure. Everyday markers of the gloomy trend towards the couch potato are plentiful and include the decreasing numbers of British schoolchildren who propel themselves to school and the lengthening time (in many cases, up to one-third of their waking life) that they spend inert in front of the television or computer games.

The converse case is often stated (and clung to with vehemence) by obese patients – namely, that their metabolism is cruelly slow and that this is the cause of their weight gain. Regrettably, this is not true: energy expenditure *increases* as weight rises [4], so that the overweight person actually has to eat *more* than someone lean in order to maintain their excess fat. There are *no* exceptions to this unpalatable restatement of the first law of thermodynamics; persuading the patient to accept this is often difficult, but essential to successful management.

Genes or environment?

Interestingly, low energy expenditure is the most important defect in certain rodents with genetic obesity, such as the *ob/ob* mouse and *fa/fa* Zucker rat discussed below. This is not the case for human obesity although some studies have suggested that young adults with the lowest levels of resting energy expenditure in some populations (e.g. the Pima Indians) are at the highest risk of becoming obese over a period of several years. In well-known animal models such as the *ob/ob* mouse and the *fa/fa* Zucker rat, obesity is entirely genetic in origin and is inherited in a classical Mendelian recessive fashion. Exceedingly rare humans also have obesity attributable to defined mutations in the genes such as those encoding leptin, its receptor and the melanocortin-4 receptor (Table 1). However, this does not apply to the common type of obesity which is a fine example of a multifactorial disease determined by the interaction between genes and the environment. Inherited factors probably account for 40–70% of susceptibility in various populations [5, 6], and apparently comprise numerous minor genes that are encouraged to declare themselves by unfavourable environmental changes. The current obesity epidemic illustrates this clearly: the doubling in prevalence in only 12 years is far too fast to be explained by changes in the genome. The very rare human mutations provide important proof of concept that these gene products play a role in normal energy homeostasis, but they do not necessarily tell us much about their role in common human obesity or their potential as targets for antiobesity drug development.

Numerous candidate genes have been investigated as possible causes for human obesity, particularly those encoding appetite-modulating neurotransmitters or their receptors, or proteins involved in energy expenditure or adipose tissue metabolism (Table 1). So far, though, none

Table 1 Some of the genetic mutations implicated in human obesity.

<i>Rare but crucial mutations</i>	
Leptin	Produced by adipose tissue, leptin reduces food intake in rats if centrally injected. Mutation on chromosome 7 found in one obese family [72].
Leptin receptor	CNS receptor for leptin, Mutation on chromosome 1 associated with three cases of human obesity [73].
Melanocortin 4 receptor	CNS receptor involved in the suppression of appetite Mutations on chromosome 18 associated with several cases of obesity [74].
Prohormone convertase 2	Converts proinsulin to insulin and C-peptide. Polymorphisms on Chromosome 20 are associated with a higher relative risk of NIDDM and obesity [75].
<i>Mutations of probably minimal clinical impact</i>	
Uncoupling proteins	UCP 2 and 3 mapped close to 11q 13 which is linked to human obesity and hyperinsulinemia [76].
Insulin Receptor Substrate	Important in cell signalling mediating the action of insulin. Candidate gene because of putative (IRS-1) involvement in insulin resistance. Recent studies of polymorphisms in African Americans showed no link with obesity [77].
β_3 -adrenoreceptor	Polymorphisms of this adrenoreceptor have been associated with an increased relative risk of obesity in some studies of Asian and Caucasian populations [78].

has emerged as a convincing player, and more subtle candidates will have to be sought: genes that encode aversion to television quiz shows could be just as strongly protective against obesity as those controlling energy expenditure in muscle.

Anti-obesity drugs in their rightful context

Effective management of obesity requires, in the first instance and above all, a multipronged attack on lifestyle (healthy eating and more exercise) which must be maintained during long-term follow-up. This can be supplemented in selected cases by appropriate weight-reducing drugs and in some cases, by surgery. It is misguided and dishonest to persuade the patient that pharmacotherapy is a miracle cure for obesity; because of the complexity of the social and physiological factors that cause and sustain obesity, this is one condition whose therapeutic armoury will never contain a magic bullet.

Drugs can only be used that are proven effective and safe and these can only be prescribed by practitioners who understand obesity and its global management, and who are prepared to select, educate and follow-up their patients.

Efficacy

Efficacy remains a stumbling block for many hopeful compounds. Some, e.g. the β_3 -adrenoceptor thermogenic agents and perhaps leptin (below), have not yet fulfilled the considerable promise which they showed in lower mammals. Ultimately, success must be defined as the restoration of normal quality and duration of life, rather than arbitrary degrees of weight loss. No sufficiently long-term studies have been performed for either of the currently available drugs, orlistat and sibutramine, and pharmaceutical companies are understandably nervous about funding and undertaking such studies. However, they may be forced into doing this, if the regulatory authorities come to demand evidence of improvements in hard end-points such as cardiovascular events or death to offset concerns about cost or uncertain benefit:risk margins.

Most physicians would accept that weight loss of 10% is useful for people whose initial BMI is 30–35 kg m⁻², as this is associated with increased insulin sensitivity that is reflected in falls in blood glucose and reduced hypoglycaemic medication requirements, in diabetic patients, together with improvements in lipid levels and often blood pressure [7–9]. However, individual responses are variable and patients with greater obesity may not show these benefits; continuing surveillance is therefore mandatory. Pragmatic criteria for assessing efficacy form the core of the guidelines of the Royal College of Physicians (RCP) [10],

which have recently been endorsed by the General Medical Council (GMC).

Safety

Safety has been the downfall of many effective drugs, a recent example being the fenfluramines which were withdrawn by the manufacturers following a series of reports linking them with low but definite incidences of primary pulmonary hypertension and sclerotic valvular heart disease [11]. Phentermine (which was often used in combination with fenfluramines) was not endorsed by the RCP report because of inadequate long-term safety data. Side-effects, some of them unpredictable until the drug enters humans, are likely to occur with many centrally acting drugs, because of the multiplicity of functions served by the neurotransmitters which they target. An interesting example is short-term memory loss with cholecystokinin [12], whose action as a satiety factor is currently being explored.

Ethical considerations

Some doctors are still giving obese patients injections of diuretics when they are not sodium-overloaded; thyroxine when they are euthyroid; banned or off-license drugs (e.g. stockpiled fenfluramine bought via the Internet); and sundry homeopathic, herbal and reflexological cures which have evaded all the tiresome hurdles that a new drug has to clear in order to prove efficacy and safety. A Belgian 'slimming clinic' has become famous because of the high presence of renal disease (interstitial fibrosis causing renal failure and urothelial cancers) among obese patients who took an unlicensed mixture of fenfluramine, diethylpropion and a Chinese herbal product; the latter was adulterated with nephrotoxic *Aristolodivia* alkaloids [13]. Fortunately, the days of sharp practice are now numbered. The prescriber's responsibilities are embodied in the RCP report and spelled out by the GMC in terms so blunt that they cannot be ignored by the unscrupulous, whether they are private specialists in Harley Street or fly by-night nomads in Bootle, a suburb of Liverpool.

Cost

Cost is another major issue, especially now that pharmacoeconomics is becoming a growth industry in its own right. On one hand, industry needs to recoup the considerable costs of drug development and marketing and make a profit; on the other, health-care providers have to rank antiobesity drugs alongside treatments for Alzheimer's disease, myocardial infarction and rheumatoid arthritis. The health benefits of reducing obesity or preventing it from getting worse may not become apparent

for many years or even decades, and the absence of long-term outcome data partly explains why obesity often finds itself far down the pecking order of diseases that are taken seriously.

Currently available antiobesity drugs

Orlistat

Orlistat (tetrahydrolipstatin) is a synthetic drug derived from a naturally occurring lipase inhibitor produced by *Streptomyces* moulds. It binds covalently to the active site of pancreatic lipase, the principal enzyme responsible for hydrolysing triglyceride, which accounts for 99% of dietary fat; it also inhibits other gut and extra-intestinal lipases but its action is restricted to the gut lumen because it is essentially nonabsorbable. Orlistat at therapeutic doses (120 mg three times daily) blocks the digestion and absorption of about 30% of dietary fat [14], and this accounts for part but not all of its weight-reducing effect; the rest may be due to the patient choosing to avoid the high-fat foods which can provoke gastrointestinal side-effects.

Dietary fat is a rational target, as it is the most energy-dense macronutrient (9 cal/g), reduces the satiating effect of foods and is encouraged by metabolic pathways to return to triglyceride in adipose tissue: fat is, in fact, fattening. Clinical trials of up to 2 years' duration have demonstrated that about one-third of patients lose over 10% of initial weight and maintain this loss throughout treatment. Long-term responders can generally be identified because they display encouraging weight loss during the first few weeks of treatment, and patients selected by having lost >5% of weight at 3 months show an impressive proportion of '10% responders' – over 40% after 12 months [15]. As with all antiobesity drugs (and most other agents aiming to treat metabolic and vascular diseases), the therapeutic effect wears off when treatment is stopped and weight tends to return to pretreatment levels; at present, orlistat is licensed only for up to 2 years. Trials confirm that orlistat also reduces weight in obese type 2 diabetic patients, a group notorious for their resistance to weight-reducing measures: about 25% lose 10% or more in weight, and this is accompanied by falls in fasting glucose of about 1–2 mmol l⁻¹ and in HbA1c of 0.5–1% [16].

Unwanted side-effects are essentially confined to the gut and consist of steatorrhoeic symptoms: fatty stools, with diarrhoea and occasionally urgency and incontinence. These problems are generally transient and mild if the patient follows standard life-style advice to avoid fat-rich foods. The absorption of fat-soluble vitamins (A, D, E and K) and of β -carotene is linked to that of triglyceride; clinical deficiencies were not seen in the clinical trials, but

vitamin supplements were given if measured levels fell below normal, and more orlistat-treated patients required supplements than controls. It is therefore possible that deficiencies of these vitamins will appear when orlistat is approved for longer-term use, although this is thought unlikely with relatively vitamin-rich Western diets. Theoretical concerns about increased gall-stone formation have not been realized in clinical practice.

Rational guidelines for the use of orlistat were drawn up by the manufacturers, who also produced readable and informative guides for prescribers and patients. Orlistat currently costs about £560 per annum.

Sibutramine

Sibutramine is a centrally acting appetite suppressant that also has mild thermogenic properties [17]. It acts by enhancing the action of two monoamines that act in the hypothalamus and other brain regions to induce negative energy deficits, namely serotonin (5-HT) and noradrenaline. When injected centrally in rodents and lower primates, both 5-HT and noradrenaline inhibit feeding and increase energy expenditure by stimulating the sympathetic outflow to the thermogenic tissues. Sibutramine blocks the reuptake of both monoamines, and therefore increases their availability in the synaptic cleft; unlike the fenfluramines, sibutramine does not stimulate the release of 5-HT from serotonergic nerve terminals. The inhibition of noradrenaline re-uptake increases sympathetic tone, consequences of which include both the desirable thermogenic effect and the potential cardiovascular side-effects of rises in blood pressure and pulse rate. Because of its actions on both monoamines, sibutramine is referred to as an 'SNRI' (serotonin/noradrenaline reuptake inhibitor).

In rodents, sibutramine causes marked weight loss that is due both to decreased food intake and enhanced energy expenditure, mainly in the densely sympathetically innervated BAT. In human trials, sibutramine showed dose related increases in weight loss in obese subjects, over the dosage range of 1–30 mg day⁻¹ [18]. At the clinically accepted dosage of 15 mg day⁻¹, average weight loss after 6 months is 7–9%, and about one third of patients lose more than 10%. Sibutramine has been shown to maintain and enhance weight loss in patients who responded well to a very-low calorie diet (VLCD) [19]; and preliminary data in obese type 3 diabetic subjects suggest that 20–25% of sibutramine treated patients can lose 10% of weight, and that many of these subjects show modest falls in fasting plasma glucose and in HbA1c [20]. Minor improvements in blood lipids have also been noted in both diabetic and non diabetic populations. As with every other antiobesity drug, cessation of its treatment is followed by weight regain in most cases.

Side-effects are mostly mild, and include dry mouth, insomnia, headache and constipation. The central sympathomimetic effects of sibutramine lead to increases in pulse rate (usually 3–5 beats min^{-1}) and in systolic and diastolic blood pressure. The latter is clearly undesirable in obese and especially type 2 diabetic patients, in whom lowering blood pressure has been shown to be more effective in preventing cardiovascular death than tight glycaemic control. In most cases however, rises in blood pressure are small (2–3 mmHg) and the overall impact on cardiovascular risk is apparently favourable, because of the benefits of weight loss and, in diabetic patients, of lower blood glucose.

Crucially, there is no evidence to date that sibutramine shares the major cardiovascular hazards of the fenfluramines, namely primary pulmonary hypertension and valvular heart disease. Although total exposure to the drug is still much less than with the fenfluramines when these gained prominence, sibutramine's mode of action is completely different from the fenfluramines and does not lead to an increase in 5-HT concentrations in the plasma or platelets [21].

Sibutramine is currently licensed in North and South America and is undergoing evaluation in countries of the European Union.

Leptin

This is undoubtedly the fastest characterized and most media-hyped hormone yet, but its roles in human physiology remain contentious. Leptin is a 14-kDa protein encoded by the *Lep* gene in humans (*ob* in mouse), expressed in adipose tissue and secreted into the bloodstream [22]. Leptin potentially has many targets – certainly many tissues express leptin receptors [23], although leptin's actions outside the rodent CNS are still largely enigmatic.

Various isoforms of leptin receptors exist, all derived by differential processing of the gene product (*LepR* in man, *OB-R* in mouse) [24]. The complete 'long' isoform (OB-Rb) spans the cell membrane, and its long cytoplasmic tail carries specific domains that activate STAT-3 and thus the JAK-STAT signalling pathway. Shorter isoforms (e.g. OB-Ra) may act as leptin transport proteins across barriers such as the choroid plexus, and also have limited signalling ability.

Leptin was named from the Greek for 'thin', because it causes weight loss in rodents. Leptin does this through concerted central actions: it both inhibits feeding and stimulates thermogenesis. This pushes the animal into negative energy balance, when fat is preferentially mobilized; theoretically, at least, leptin therefore has highly favourable antiobesity actions. In rodents, it seems to function physiologically to regulate body weight and fat mass, by completing a homeostatic loop between fat and

brain in which the negative-feedback link is leptin's actions that induce net energy loss and mobilization of fat (Figure 1). The importance of leptin in rodents is underlined by the morbid obesity, due to both overeating and decreased energy expenditure, that occurs when this loop is disrupted by mutations that inactivate either leptin itself (the *ob/ob* mouse) or its receptors (*db/db* mouse, *fa/fa* Zucker rat) [24].

Leptin acts on many neuronal systems in the hypothalamus and elsewhere in the CNS that are implicated in controlling food intake and energy expenditure. Its known targets include hypothalamic neurones expressing NPY, a powerful appetite-stimulating and antithermogenic peptide. These are inhibited by leptin. Conversely, leptin stimulates neurones that produce corticotrophin-releasing factor (CRF) and α -melanocyte stimulating hormone (α -MSH), both of which inhibit feeding while stimulating energy expenditure. This multiplicity of targets probably explains why natural 'knockout' of leptin in the *ob/ob* mouse has such devastating effects on energy balance: knockout of its individual target neuropeptides (e.g. neuropeptide Y, NPY) generally has less impressive effects, presumably because other neuronal systems can assume more important roles and partly compensate for the disrupted system.

Leptin in human obesity The relevance of leptin to common human obesity is uncertain. This is in sharp contrast to the extremely rare cases of mutations in the *Lep* or *Lep-R* genes (analogous to *ob* and *db*) which cause dramatic and early onset morbid obesity (Table 1); one patient with a *Lep* mutation and the virtual absence of biologically active leptin has been treated with recombinant human leptin, resulting in prompt and marked loss of body fat [25].

In all other people, as in nonmutant rodents, plasma leptin levels rise roughly in proportion to body fat mass, although there is wide individual variation around the regression line, with up to 10-fold range in plasma leptin levels among individuals of BMI > 30 kg m^{-2} [26]. It is possible that the persistence of obesity in the presence of high leptin levels indicates that leptin is trying but failing to exert its weight-reducing actions, a situation speculatively termed 'leptin resistance' by analogy with the compensatory hyperinsulinaemia that accompanies insulin-resistant states, including obesity itself. There is evidence that partial 'resistance' to leptin's hypophagic action can be induced in rats that become obese through over-eating a palatable diet [27]; but there is no way of testing this hypothesis in man because no measures of leptin action (analogous to the hypoglycaemic effect of insulin) have yet been identified. Leptin is transported across the choroid plexus into the cerebrospinal fluid (CSF) of mammals, and CSF levels in grossly obese people are lower than would be predicted in proportion to their raised plasma levels [28].

Figure 1 Diagrammatic representation of the effects of leptin in energy homeostasis.

Figure 2 Hypothetical dose-response curves for the anti-obesity action of leptin. In both men and rodents, the total absence of leptin causes hyperphagia and early-onset morbid obesity, proving that leptin is involved in regulating energy balance. In rodents, food intake and body weight fall as plasma leptin levels are increased through the physiological and into the pharmacological range. The shape of the dose-response curve in man is unknown, but leptin levels in the physiological and pharmacological range do not appear to decrease fat mass as powerfully as in rodents. This blunting of leptin action could be due to physiological 'leptin resistance' or the overwhelming effect of psychosocial factors in human eating behaviour.

However, the cause of this apparent failure of transport is unknown, as is its possible relevance to 'leptin resistance'.

The key (and imponderable) issue is the shape of the dose-response curve to leptin in humans (Figure 2), which must obviously remain a purely hypothetical concept until some way of measuring a response to leptin can be found. In both rodents and humans, the complete absence of leptin or its signal leads to obesity, but the magnitude or the responses to 'physiological' and 'pharmacological' leptin levels may be quite different. In rodents, food intake falls and weight is lost as plasma leptin rises through the physiological range, and would probably produce a reasonably steep sigmoidal curve. In man, clinical trials of leptin have not shown such a dramatic effect, possibly because of all the other social and psychological factors that moderate human feeding behaviour; it is unusual for people in affluent Westernised societies to eat because their nutritional state is under threat. The effective dose-response curve in humans may therefore be flatter and possibly right-shifted compared with that in rodents.

Clinical experience with leptin Initial trials of subcutaneously injected human leptin in human obesity have not shown the hoped-for miraculous therapeutic response, although patients on high dose leptin achieved weight loss of

–7.1 kg from baseline at 24 weeks [29]. It is therefore possible that some obese patients are relatively leptin-deficient, even though their absolute leptin levels may be substantially higher than normal values; such patients may therefore benefit from leptin supplementation.

One practical problem with this trial was that the active leptin, but not placebo, caused obvious local injection reactions in some cases. The study was therefore not entirely double-blind, and this could have biased the outcome in favour of active treatments: obesity is a condition in which nonpharmacological trial effects can be notoriously powerful, at least in the short term.

At present, modified and truncated leptin analogues and low molecular-weight ligands at leptin receptors (including nonpeptide molecules) are under development. These may have improved pharmacokinetic properties, including enhanced transport into the CNS, and possibly good enough bioavailability to be given by mouth; long-term compliance with oral medication is already problematic in obesity and many obese patients might not continue to take injections for long enough to enjoy the clinical benefits of lasting weight reduction. Developments in this area are awaited with keen interest.

Potential CNS targets for novel antiobesity drugs

Neuropeptide Y (NPY)

NPY, a 36-amino acid relative of pancreatic polypeptide, is one of the most potent orexigenic peptides in mammalian brains. In rodents, it is expressed at high levels by neurones in the hypothalamic arcuate nucleus (ARC) that project to major appetite-controlling regions, notably the paraventricular nucleus (PVN) [30]. Feeding is powerfully stimulated when NPY or its N-terminally truncated analogues (e.g. NPY 3–36) are injected into the PVN or the adjacent perifornical region of the lateral hypothalamic area (PF-LHA) of rats [31]. The sympathetic outflow to thermogenic tissues including BAT is also inhibited [32], resulting in a co-ordinated shift towards positive energy balance which rapidly induces obesity: fat mass doubles within a few days during continuing NPY administration.

On a molar basis, NPY and its analogues are the most potent central appetite stimulants known and its ability to induce obesity so rapidly is unique; moreover, enhanced NPY neuronal activity (due to loss of inhibition by leptin) apparently contributes to overeating and obesity in *fa/fa* rats and *ob/ob* mice [33, 34]. These properties make it an obvious choice for antiobesity drug development. However, NPY's wide distribution throughout the brain and its impressive list of suggested physiological functions (including arousal, cardiovascular regulation and

antiepileptogenic actions) make it crucial to target selectively the specific population of NPY neurones or the 'feeding' receptor that mediate its hyperphagic effect.

So far, six NPY receptors have been cloned, all belonging to the 7-transmembrane domain, G-protein linked family. Most evidence points to the Y5 type as the 'feeding' receptor; a population of these receptors in the exquisitely NPY-sensitive PF-LHA may be particularly important [35]. A high-affinity, selective Y5 antagonist (CGP 71683 A) given intraperitoneally in various rat models of obesity inhibits feeding; this effect wears off after a few days of continuing administration, but the weight curve of treated animals remains below that of controls [36]. Curiously, the Y5 knockout mouse does not show the predicted hypophagia or weight loss [37], which merely reinforces our personal prejudice that the knockout approach is clever technology, but inappropriate for studying physiological systems based on multiple homeostatic loops that communicate with each other.

Other approaches to manipulating NPY therapeutically may include antagonists based on modified Y1 antagonists and Y2 agonists. Some compounds with potent Y1 antagonist properties (e.g. BW1229U91) inhibit feeding in the rat, and recent studies have identified NPY receptors in the thalamus that are blocked by BW1229U91 [38] but not by classical Y1 antagonists (King P J, *et al.* unpublished data); these may represent atypical Y1-like receptors (or perhaps a new class of NPY receptor) but are found in extrahypothalamic sites that are not usually associated with feeding behaviour. Y2 receptors are expressed by NPY neurones in the ARC and may act as autoreceptors that inhibit NPY release; the view that Y2 agonists may have antiobesity properties is supported by the Y2 knockout mouse, which becomes obese [39].

Melanocortin system

Melanocortinergic neurones and their targets have emerged recently as an exciting candidates in the hypothalamic regulation of energy balance. Neurones expressing pro-opiomelanocortin (the common precursor for opioid peptides, melanocyte-stimulating hormone (MSH) and ACTH) are found in the ARC of rodents and project to many sites in and beyond the hypothalamus, where various types of melanocortin receptor are found (Figure 3.) [40]. α -MSH appears to be the ligand involved in feeding, and it acts mainly on the melanocortin-4 receptor (MC4-R) to inhibit feeding, stimulate thermogenesis and cause loss of fat [41]. The importance of the melanocortin system in energy balance was pointed to by a strikingly fat and yellow mutant A^y mouse; the mutation affects the promoter region of the *agouti* gene, which causes the 131-residue 'agouti' peptide to be expressed

Figure 3 Diagram showing binding of [^{125}I]NDP-MSH in the rat hypothalamus. Binding is most intense at the hypothalamic ventromedial (VMH) and arcuate nuclei (ARC) and the median eminence (ME). With lower levels in the medial habenulla (MHb). These areas are known to be important in the control of food intake.

ectopically in the hypothalamus and at high levels in the hair follicles. Agouti is an endogenous antagonist of melanocortin receptors: in the hair follicle, it blocks α -MSH action at the MC1-R (which normally stimulates black melanin pigment synthesis), while in the hypothalamus, it inhibits activation of the MC4-R [42]. Interestingly, NPY neurones in the ARC normally express another endogenous MC4-R antagonist ('agouti-gene related peptide', or AGRP) which also potently stimulates feeding and induces obesity [43]. Reassuringly, for believers in the transgenic approach, obesity develops in mice that either re-express AGRP or that have the MC4-R gene knocked out [44].

Potential weight-reducing drugs could therefore include α -MSH analogues and particularly selective ligands at the MC4-R. The α -MSH analogue MT-II reduces food intake and body weight [45] and has other unrelated properties that are ripe for exploitation: namely, tanning of the skin and penile erection. To avoid potential distractions, antiobesity drugs should probably focus closely on the MC4-R, especially as a highly selective MC4-R antagonist (HSO14) has recently been shown to induce sustained hyperphagia and obesity [46]. The molecular design of agonists appears to be more challenging than for antagonists, but high-affinity, selective MC4-R agonists are undoubtedly already under development.

Orexins

Orexins A and B are recently described peptides (33 and 28 residues, respectively), derived from the common precursor, prepro-orexin, which is expressed only in specific neurones lying in the LHA, including the perifornical area (PF) which is so sensitive to NPY [47]. Prepro-orexin is identical to 'preprohypocretin', which can yield two other peptides called hypocretin-1 and -2, whose predicted amino-acid sequences include those of orexin A and B, respectively [48]. Orexin neurones project to, and receive neural inputs from, many hypothalamic areas involved in regulating feeding, and are also connected reciprocally with the nucleus of the solitary tract (NTS), which relays vagal inputs from the viscera that include satiety signals (portal-vein glucose and gastric distension). Two orexin receptors have been identified in many brain regions: OX-1, which is selective for orexin A, and OX-2 which recognizes both (Figure 4) [49, 50].

Orexins were first named for their ability to stimulate feeding when injected centrally, but this hyperphagic effect appears to be transient and does not lead to obesity [51]; furthermore, the appetite-stimulating effect of orexin-B appears to be weak and possibly negligible. Current evidence suggests that the orexin neurones may drive feeding in rats, although under the specific conditions

Figure 4 Immunohistochemical labelling (blue staining) of Orexin-A (upper panel) and MCH (lower panel) in the hypothalamus of rats made hypoglycaemic with insulin. 3V = 3rd ventricle; f = fornix; mt = mammillothalamic tract.

when blood glucose is low or falling, and when the gut is empty [52, 53]. This puts them in a potentially important position as short-term regulators of feeding, perhaps being stimulated by the falls in glucose that precede feeding, and then being switched off by satiety signals relayed via the NTS.

Orexin antagonists are under development and it will be interesting to see whether they reduce meal size or duration, effects which could be extremely useful for future weight-reducing drugs. Selectivity may be a problem, as with all CNS targets: the extensive wiring of orexin neurons makes it likely that they serve multiple functions. One area heavily innervated by orexin terminals is the locus coeruleus, which is critical in maintaining wakefulness – mutations of the OX-2 receptor have been recently shown to cause narcolepsy in dogs [54], and arousal is also disturbed in the orexin knockout mouse [55].

Other CNS targets

Some of these are shown in Table 2. They include the appetite-stimulating peptides melanin-concentrating hormone (MCH), galanin and opioids such as dynorphin; and the appetite-inhibiting neurotransmitters, serotonin, corticotrophin-releasing factor (CRF) and bombesin. MCH is expressed in the LHA and up-regulated in the *ob/ob* mouse [56], which also shows disturbances in many other peptides; MCH stimulates feeding in the short term and its overall physiological importance is not certain. Its receptor is now known to be the G-protein linked 'orphan' receptor, SLC-1 [57]. Galanin was previously suggested to stimulate fat intake selectively, a potentially exciting property, given the pivotal role of fat-rich foods in human obesity, but this does not now seem to be the case, and sustained administration of galanin does not induce obesity [58].

Development is under way for selective CRF-2 receptor agonists (to avoid effects on ACTH secretion, regulated by the CRF-1 receptor), and agonists at the GRP receptor which mediates the appetite-suppressing

Table 2 Neurotransmitters known to influence energy balance.

Appetite stimulating		Appetite suppressing	
Neurotransmitter	Receptor	Neurotransmitter	Receptor
NPY	[Y5?Y1]	α -MSH	[MC4-R]
Orexin A	[Ox1 Ox2]	CRF	[CRF-2]
MCH	[SCC-1]	GLP-1	[GL-1]
Galanin	[Gal-1]	CCK	[CCK _A CCK _B]
Dynorphins	[κ]	Serotonin	[5HT _{2c}]
		Bombesin/GRP	[BRS-3/GRP-R]

effect of bombesin and its human homologue, gastrin-releasing peptide [59].

Another recently identified CNS target is the imidazoline (I-1) receptor which is expressed in the lateral medulla and is implicated in the central regulation of blood pressure. The antihypertensive drug moxonidine, an I-1 agonist, also has striking antiobesity effects, at least in the *fa/fa* Zucker and spontaneously hypertensive (SHR) rats [60]. Moxonidine both reduces food intake and stimulates BAT, which suggests a highly selective effect on different divisions of the sympathetic outflow as its hypotensive action is attributed to a central reduction in sympathetic tone to the cardiovascular system. Major antiobesity effects have not been apparent from clinical experience with moxonidine, but the package of beneficial effects in obese rats is impressive and points to the need for further exploration of I-1 agonists.

Satiety factors

Cholecystokinin (CCK), one of the longest established satiety hormones, is released into the bloodstream from the small intestine by food. It appears to act at a number of levels, with specific classes of CCK receptor being expressed in the gut (CCK_A, e.g. the pylorus, which is closed by CCK) and the brain (CCK_B, e.g. in the hypothalamus) [61]. Its satiating effect, demonstrable in normal man as well as lower mammals, may be due to increased gastric distension following closure of the pylorus, which is sensed by vagal afferents that also carry CCK_A receptors; interestingly, the ascending pathway through the NTS to the lateral hypothalamus also involves CCK, acting here as a neurotransmitter on CCK_B receptors. Both CCK_A and CCK_B agonists are being explored as potential antiobesity drugs; another novel approach is to develop inhibitors of the serine peptidase that normally degrades CCK: a prototype compound inhibits feeding in rats [62].

Glucagon-like peptide-1 is a peptide, which is also released from the gut after eating and is also expressed in the CNS, in brainstem neurones that project to the hypothalamus. Like CCK, it may operate at multiple levels, and is also implicated as an 'incretin', helping to augment insulin secretion after eating. GLP-1 receptors are expressed in the PVN, and feeding is stimulated by central injection of a naturally occurring GLP-1 antagonist (exendin 9–39) [63], intriguingly and possibly riskily isolated from the venom of the poisonous Gila monster). This suggests that GLP-1 acts tonically to restrain feeding.

Clinical trials of GLP-1, given by continuous intravenous or subcutaneous infusion, have demonstrated both satiating and glucose-lowering actions in type 2 diabetic patients [64], although long-term effects on body weight and fat mass are not yet known. Buccal forms of GLP-1

(to avoid proteolytic degradation in the gut) are being tested, and an inhibitor of dipeptidyl dipeptidase-IV (DPP-IV), the enzyme which degrades GLP-1, has been shown to decrease food intake [65], similarly to the effects of prolonging CCK survival by blocking its degradation.

Thermogenic drugs

The notion of pharmacological enhancement of energy expenditure to promote weight loss is an old one. Many early 'slimming pills' included thyroid extract to increase metabolic weight and promote weight loss, although the associated side-effects have now consigned this treatment to the history books.

Animal research has shown that the 'atypical' β_3 -adrenoceptors that are highly expressed in brown adipose tissue (BAT) play an important part in controlling metabolic rate. Activation of β_3 -adrenoreceptors stimulates lipolysis in brown and white adipocytes and leads to production of the free fatty acids that act as thermogenic fuels [66]. One of the primary mechanisms for the increase in basal metabolic rate seems to be the up-regulation of uncoupling proteins in the brown adipocyte, which is stimulated by noradrenaline released from sympathetic nerve terminals in BAT and acting via the β_3 -adrenoceptor [67]. Uncoupling proteins (UCPs) are mitochondrial transmembrane proteins that collapse the hydrogen gradient and thus uncouple oxidative phosphorylation, i.e. reduce ATP production, with the generation of heat as a reaction byproduct – hence the term thermogenesis. The first described UCP (UCP-1) is confined to BAT, which is very sparse in adult humans. For a long time the role of these proteins in human metabolism seemed doubtful, but the discovery of two new UCPs that more widely distributed in man has sparked renewed interest in this area. UCP-2 is expressed in many tissues including muscle white fat and liver, while UCP-3 is largely restricted to BAT and skeletal muscle [68].

β_3 -adrenoceptor agonists (structurally similar to the catecholamines that have high affinity at the rodent β_3 -receptor) increase energy expenditure in BAT and other tissues and cause mobilization of fat and weight loss. The optimal compounds show high β_3 selectivity, with few side-effects mediated by other β -receptor subtypes (e.g. tachycardia, via β_1); some also improve insulin sensitivity and stimulate insulin secretion. However, human trials of β_3 -adrenoreceptor agonists developed in rats showed less impressive antiobesity effects and were complicated by β_1 and β_2 side-effects such as tremor and tachycardia [69]. Further work has now shown that in fact human and rodent β_3 -adrenoreceptors differ considerably pharmacologically, and that compounds tailored to the rat or mouse receptor have low affinity and poor β_3 receptor selectivity in man. Trials of a new human-specific β_3 -adrenoreceptor

agonist, L-755 507 have shown encouraging results in primates [70].

In Scandinavia particularly, the thermogenic effects of ephedrine and caffeine combinations (60 mg and 600 mg, respectively) have been widely used to promote weight loss, although 75% of the weight loss produced by ephedrine may be due to its anorectic properties [71]. Thermogenesis is thought to be induced by nonspecific adrenoreceptor stimulation, which also produces the associated side-effects such as dizziness, tremor, agitation and palpitations.

Conclusion

In this article, we have attempted to provide a background for the current theories on the aetiology of obesity, as well as describing the newer drug therapies being developed to combat this ever-growing problem. Despite still not being able to control the overeating of the majority of the population we are now able to target individuals at risk of developing obesity-associated morbidity and can offer effective treatment. Of course, the treatment of obesity itself must be centred on health education and the promotion of sensible eating habits associated with exercise and behaviour modification. However, there will always remain a subgroup of obese individuals in whom simple measures alone will not correct weight, and in whom the introduction of novel, safer and more effective pharmaceutical agents to control weight will increase life expectancy and quality of life.

The new generation of antiobesity drugs offer new hope in the management of obesity, but there is unlikely ever to be a panacea. Current evidence suggests that Government policy and investment should be directed to active health education and promotion to prevent weight gain occurring and thus prevent the costs of treating obesity and its consequences from spiralling out of control.

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