Drug Treatment of Obesity: Established and Emerging Therapies

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Abstract: Available anti-obesity pharmacotherapy options remain very limited. The development of more effective drugs has become a priority. The potential strategies to achieve weight loss are to reduce energy intake, by stimulating anorexigenic signals or by blocking orexigenic signals, and to increase energy expenditure. This review will focus on approved obesity medications, as well as potential new pharmacological treatment options.

Key Words: Obesity, drug treatment, orlistat, sibutramine, rimonabant, leptin, ghrelin.

INTRODUCTION

Energy balance in humans is the result of complex interactions between neuroanatomical, genetic, endocrinological, pathophysiological, nutritional, physical, psychological and social-environmental factors. Obesity and overweight are highly prevalent chronic conditions and are associated with premature mortality, chronic morbidity and increased healthcare use. Long-term maintenance of weight loss is difficult due to the fact that, in response to alterations in body adiposity, the brain triggers compensatory physiologic adaptations that resist weight change.

Available pharmacotherapy options remain very limited. At the time of publication, only two medications (orlistat and sibutramine) are approved for weight loss and weight maintenance in the USA and Europe. Rimonabant was approved in some European countries until very recently. Orlistat is a triacylglycerol lipase inhibitor that works in the intestinal lumen to reduce dietary fat absorption by about 30%. Sibutramine is a serotonin-norepinephrine reuptake inhibitor that reduces appetite. Ritmonabant is a selective blocker of the cannabinoid receptor CB1 which has been shown to be involved in the central and peripheral regulation of food intake. Several older medications are approved in certain countries for short-term use in weight loss.

The new understanding of the biology of weight regulation has provided a wide range of promising potential drug targets. The three potential strategies to achieve weight loss are to reduce energy intake, by stimulating anorexigenic signals or by blocking orexigenic signals, and to increase energy expenditure. Gut hormones and/or their derivates might provide the advantage of targeting specific appetite pathways within the brain without producing unacceptable side effects. It seems that the desired degree of effectiveness will most likely be achieved, with less toxicity, through the use of combinations of treatment.

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ESTABLISHED THERAPIES

Losses of 5-10% of initial bodyweight are associated with significant improvements in cardiovascular risk factors and reductions in the incidence of type 2 diabetes mellitus. Approved anti-obesity therapies promote smaller mean weight losses which are also associated with improvements in cardiovascular risks factors, but it has to be shown that this translates into reduction of morbidity and mortality. Some authors have drawn attention to the fact that substantial weight loss might have some unexpected effects on health, which emphasizes the importance of caution when attempting to achieve weight loss [1].

The U.S. Food and Drug Administration (FDA) recommends pharmacotherapy for weight loss when lifestyle interventions (diet, exercise and behavioural therapy) fail and the body mass index (BMI) is $\geq 30 kg/m^2$ with no concomitant obesity-related risk factors, or if the BMI is ≥ 27 kg/m^2 and the patient has at least one obesity-related risk factor. Adherence to lifestyle interventions (diet, exercise and behavioural therapy) should continue during pharmacological treatment.

Orlistat

Orlistat is a gastrointestinal lipase inhibitor; therefore, it is a non-centrally acting agent. It decreases fat absorption by binding to pancreatic lipase, blocking hydrolyses of triglycerides into fatty acids and monoglycerides, and increasing faecal fat excretion by 30%. Orlistat was approved by the FDA in 1999 for weight loss and weight maintenance.

Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2- oxetanyl] methyl]-dodecyl ester. Its empirical formula is $C_{29}H_{53}NO_5$, and its molecular weight is 495.7 (Fig. **1**). It is a single diastereomeric molecule that contains four chiral centres, with a negative optical rotation in ethanol at 529 nm.

Intestinal absorption of orlistat is minimal; it undergoes some metabolism within gastrointestinal wall to inactive metabolites and is eliminated in the faeces, mostly unchanged. In several randomized clinical trials (RCTs), the weight loss achieved was about 3% greater for subjects

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taking orlistat than for those taking placebo. After one year of treatment, mean body weight loss was about 2.89 kg greater in the active group than in the control group [2-4]. A reduced incidence of type 2 diabetes was demonstrated in patients who received orlistat for 4 years in the Xendos study [5].

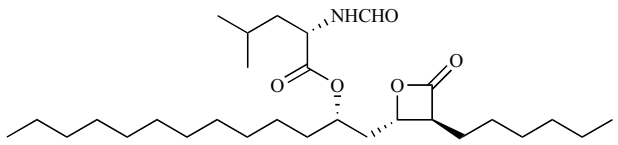

Fig. (1). Chemical structure of orlistat.

Orlistat produces significant gastrointestinal side effects, due to its mechanism of action (oily faecal spotting, flatus with discharge, faecal urgency, oily stools, increased defecation, faecal incontinence, abdominal pain) in 15-30% of the patients undergoing treatment, which tend to disappear with time if the patient adheres to a low fat diet. Losses of fat-soluble vitamins have been reported with orlistat.

Sibutramine

Sibutramine is a centrally acting agent that inhibits serotonin and norepinephrine reuptake. Originally developed as antidepressant, it reduces food intake by reducing appetite. It was approved by the FDA for the treatment of obesity in 1997.

Chemically, the active ingredient is a racemic mixture of the (+) and (-) enantiomers of cyclobutanemethanamine, 1-(4-chlorophenyl)-N,N-dimethyl-α-(2-methylpropyl)-, hydrochloride, monohydrate, and has an empirical formula of $C_{17}H_{29}Cl_2NO$ (Fig. **2**). Its molecular weight is 334.33.

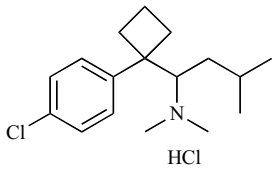

Fig. (2). Chemical structure of sibutramine.

Sibutramine is absorbed well from the gastrointestinal tract, but undergoes considerable first-pass metabolism, which reduces its bioavailability. It is metabolized by cytochrome P450 isoenzyme CYP3A4, resulting in two active primary and secondary amines (called active metabolites 1 and 2). The following metabolic pathway mainly results in two inactive conjugated hydroxylated metabolites (called metabolites 5 and 6), which are mainly excreted in the urine.

Long-term RCTs of sibutramine (10-20 mg/d) in combination with a reduced calorie diet have demonstrated modest, although significant, weight loss compared with placebo over 1-2 years and maintenance of weight loss. In several randomized clinical trials, weight loss was about 5% greater for subjects taking sibutramine than for those taking placebo. Maximal weight loss was achieved within the first 6 months of treatment and was dose related. Mean weight loss after 6 months of sibutramine 10 mg/d in combination with a low calorie diet was 7.5 kg compared with 3.6 kg for the placebo; sibutramine 15 mg resulted in 10.3 kg weight loss, compared with 1.3 kg in placebo recipients [2-4].

Due to the potential to increase blood pressure and heart rate, it is recommended that these parameters are monitored in patients taking sibutramine, and its use is contraindicated in patients with uncontrolled or poorly controlled hypertension. It has been suggested that a progressive tri-therapy intervention with sibutramine-diet-exercise enhances weight loss without inducing increases in heart rate and blood pressure [6].

Rimonabant

Rimonabant is a selective blocker of type 1 endocannabinoid receptors that was investigated as an anti-obesity drug and for smoking cessation. Cannabinoid receptors participate in the physiological modulation of many central and peripheral functions [7]. It is an appetite suppressant. In 2006, the European Commission approved the sale of rimonabant in the 25-member European Union. While this manuscript was being prepared, rimonabant was withdrawn from European markets because of concerns over suicide. The FDA has not approved the drug due to concerns over suicide, depression and other related side effects associated with use of the drug.

It is N-(Piperidin-1-il)-5-(4-chlorphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-carboxamide (Fig. **3**). The degree of intestinal absorption for rimonabant is unknown, but it undergoes hepatic metabolism (cytochrome 3A4 and aminohydrolase pathways) to inactive metabolites. It has biliary and faecal excretion.

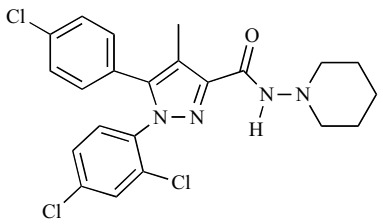

Fig. (3). Chemical structure of rimonabant.

At present, only the results of three one-year and one two-year trials have been published. Subjects taking rimonabant lost about 5% more weight than those taking placebo. In the one-year trials, treatment with rimonabant (20mg) caused significantly greater weight loss than treatment with placebo (mean 6.6 ± 7.2 kg *vs.* 1.8 ± 6.4 kg, respectively). In the active treatment group significantly greater improvements in waist circumference, HDLc, triglycerides, insulin resistance and prevalence of the metabolic syndrome were observed. Similar results were reported in the two-year trial [2-4]. Rimonabant has been shown to cause weight loss, significant improvements of cardiovascular risks factors (dyslipidemia, blood pressure and waist circumference) and reductions of HbA1c in obese type 2 diabetic patients. It is possible that rimonabant has beneficial effects on HDLc and triglyceride levels independent of weight loss. This is probably related to its direct effects on adipose tissue, liver and muscle.

The most frequent side effects were nausea, dizziness, diarrhoea, insomnia and psychiatric disorders (mainly de-

pression and anxiety). 13-16% of the patients included in clinical trials abandoned because of side effects. It is important to point out that in clinical trials patient inclusion criteria was highly selective, in order to exclude subjects with psychiatric disorders.

Phentermine

Phentermine is dimethylphenethylamine hydrochloride (Fig. **4**). It is an amphetamine-like analogue, indirectly acting sympathomimetic agents that increase norepinephrine levels in the synaptic cleft, resulting in the stimulation of β_2-adrenergic receptors and inhibition of feeding. Phentermine has also been reported to inhibit monoamine oxidase and increase the effects of serotonin, by inhibiting its pulmonary clearance.

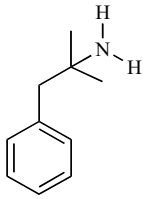

Fig. (4). Chemical structure of phentermine.

Since the drug was approved in 1959, practically no clinical studies have been carried out [2]. The longest double-blind RCT of phentermine monotherapy had a duration of 36 weeks. Overall, 16-36 weeks of treatment with phentermine in combination with a restricted-calorie diet has led to losses of 5-15% of initial body weight in 60% of patients. The most recent study combined phentermine with fenfluramine or dexfenfluramine, known as Fen-Phen. After several cases of heart valve disease in Fen-Phen users, fenfluramine and dexfenfluramine were taken off the market at the request of the FDA. Phentermine is available in many countries, including the U.S. However, because it is similar to amphetamines, individuals may develop an addiction to it. Phentermine should be used short-term (usually interpreted as 'up to 12 weeks'). In the United States, it is classified as a schedule IV controlled substance under the Controlled Substances Act.

Phentermine is relatively well tolerated. It can produce side effects consistent with its catecholamine-releasing properties (tachycardia, elevated blood pressure, insomnia and restlessness), but the incidence and magnitude of these appear to be less than with amphetamines. Additionally, phentermine has the potential to cause physical and psychological dependence.

EMERGING THERAPIES

Approved anti-obesity therapies promote mean weight losses of 3-5% of initial body weight. Most patients are still overweight or obese after treatment, and most regain weight after drug withdrawal. As a result, the development of new and more effective drugs has become a research priority.

Obesity results from a chronic energetic misbalance in which energy intake exceeds energy expenditure. Therefore, the three potential strategies to achieve weight loss are: 1) to reduce energy intake, by stimulating anorexigenic signals or by blocking orexigenic signals, and 2) to increase energy expenditure (Table **1**). All of these strategies are being actively investigated, although it is not likely that a solution will be available in the near future. The identification of a potential target is a long way from the synthesis of a compound that may become a drug.

Table 1. Potential Antiobesity Therapies

Drugs that stimulate anorexigenic signals:
Leptin receptor superagonists
Peptides downstream of leptin: agonists of melanocortin receptor-4
Ciliary neurotrophic factor analogues
Agonists of 5-HT
Drugs that inhibit orexigenic signals:
Neuropeptide Y receptor antagonists
Melanin-concentrating hormone-1 receptor antagonists
Somatostatin analogues
Gastrointestinal peptides, as drug targets:
GLP-1 receptor agonists
Peptide YY 3-36 analogues
Ghrelin receptor antagonists or inverse agonists
Oxyntomodulin analogues
Drugs that increase energy expenditure:
Beta-adrenergic agonists
Growth hormone receptor agonists

Although signalling interactions are far from being completely understood, very briefly the hypothalamus is a primary site for the integration of several factors of central and peripheral origin for the regulation of energy homeostasis (Fig. **5**) [8]. The status of energy stores is conveyed to the central nervous system by adiposity-associated hormones (leptin and insulin) and possibly some gastrointestinal peptide hormones, such as ghrelin. In the arcuate nucleus, leptin and insulin stimulate the activity of neurons that express the catabolic neuropeptide precursor proopiomelanocortin (POMC) and inhibit neurons that produce the anabolic mediators neuropeptide Y (NPY) and the agouti-related protein (Agrp). Several of these groups of neurons are interconnected at different levels, so that the activation of a group inhibits other neurons and vice-versa. Information about short-term modifications in nutrient status is conveyed to the brain through meal-related gastrointestinal hormone responses, variations in levels of nutrient content and gastric distension. This information influences the size and frequency of each individual eating episode. With the exception of ghrelin, which is thought to promote meal initiation, gastrointestinal signals contribute to satiation and meal termination. This feedback system, together with genetic, psychological and social-environmental factors, interacts to elicit endocrine,

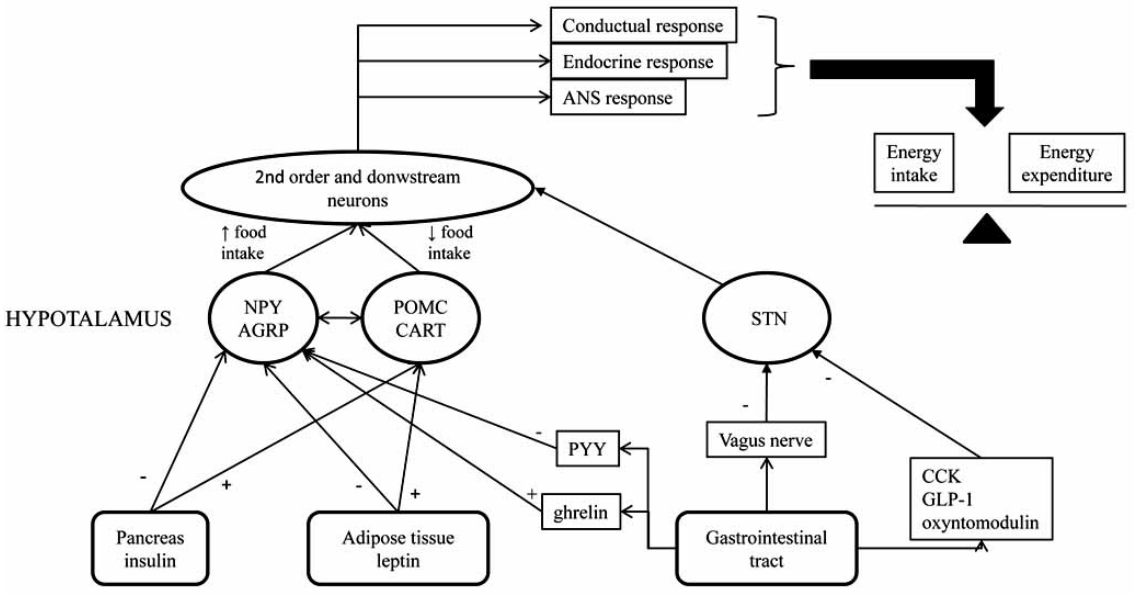

Fig. (5). Simplified representation of control of food intake. PYY: peptide YY; CCK: cholecystokinin; NPY: neuropeptide Y; AGRP: Agouti-related protein; POMC: proopiomelanocortin; CART: cocaine and amphetamine-related transcript; SNT: solitary tract nucleus; ANS: autonomic nervous system.

autonomic and behavioural responses that determine body weight.

STIMULATION OF ANOREXIGENIC SIGNALS

Leptin

Leptin is a versatile 16 kDa peptide hormone, with a tertiary structure resembling that of members of the long-chain helical cytokine family. It was originally thought to act only as a satiety factor, although there is considerable evidence for systemic effects of leptin on body mass control, reproduction, angiogenesis, immunity, wound healing, bone remodelling and cardiovascular function, as well as on specific metabolic pathways. At least five isoforms of leptin receptor exist, primarily because of alternate splicing. The longest form is capable of full signal transduction. The short forms may serve as leptin binding proteins and play a role in leptin transporting across the blood-brain barrier. The mechanism by which leptin modulates energy balance involves many hypothalamic neuropeptides including neuropeptide Y (NPY), the melanocortin system, melanocyte-concentrating hormone and cocaine- and amphetamine-regulated transcript [9].

Interest in leptin as anti-obesity drug was reduced when elevated levels were noted in the majority of obese individuals [10]. Subsequent research has shown that most cases of obesity are associated with leptin insensitivity or resistance, rather than leptin deficiency. Obese and non-obese subjects have similar central leptin levels, which suggests that transport to CNS, rather than intrinsic responsiveness to leptin, may be rate limiting for leptin activity in the obese state [11]. It is therefore necessary to develop a treatment that overcomes leptin insensitivity or bypasses normal central leptin functioning, for example by developing novel forms of leptin with stronger physiological properties [12]. The peptides downstream of leptin constitute another possible target for therapeutic interventions. Finally, another strategy is to target genes that are involved in leptin functioning, such as negative regulators of leptin signalling SOCS3 and PTP1B.

The literature strongly suggests that leptin resistance is due to a decreased transport of leptin across the blood-brain barrier in obese humans and rodents. The main cause of this resistance appears to be an impairment in the activity of the transporter rather than simply saturation at higher doses [13]. In fact, the transport mechanism into the brain is saturated at relatively low plasma leptin concentrations. The nose provides an effective way for delivering neuropeptides to the central nervous system, bypassing the blood-brain barrier and avoiding systemic side effects. In obesity, leptin-receptor signalling is blunted in brain areas critical to energy homeostasis, even when leptin is injected directly into the brain [14]. This problem could be addressed by creating leptin-receptor superagonists, although the development of synthetic leptin-receptor agonists is in preclinical stages.

The peptides downstream of leptin constitute another possible target for therapeutic interventions in obesity. Proopiomelanocortin (POMC) is the first key intermediary of leptin-receptor signalling. POMC is a complex polypeptide precursor which is cleaved into smaller biologically active peptides. Data from human genetic and murine studies show that an intact central melanocortin signalling pathway is critical for normal energy homoeostasis [15, 16], although

POMC-derived peptides are also involved in adrenal physiology and other functions. Cleavage of POMC produces biologically active peptides such as the melanocortins, α-, β- and γ -melanocyte-stimulating hormone. α-MSH activates melanocortin-3 and melanocortin-4 receptors (Mc3r, Mc4r) to exert catabolic effects. Specifically designed MC4R agonists are being investigated for the potential treatment of obesity. Ro-27-3225 (Bu-His-Phe-Arg-Trp-Gly-NH_2), a non-selective human MC4R pentapeptide agonist, was reported to be capable of reducing food intake and weight gain in *ob/ob* mice [17]. Using it as a template, systematic replacement of the residues was used to identify selective MC4R agonists, but the level of efficacy of these compounds was not reported. Several companies have MC4R agonists that are being investigated in the treatment of obesity, including piperazinebenzylamines, piperazinethylamines, piperazine-sulfonamides and other small-molecule agonists [18]. The effects of POMC on food intake and body weight and current developments in potential therapies to manipulate this pathway have recently been reviewed [19].

Recent data suggest that altered adipose tissue factors could have an important role in lipolysis regulation [20].

Ciliary Neurotrophic Factor

Ciliary neurotrophic factor (CNTF) is a 22-kDa protein that is expressed in Schwann cells in the peripheral and astrocytes in the central nervous system. CNTF itself lacks a classical signal peptide sequence of a secreted protein. The CNTF receptor complex is most closely related to, and shares subunits with the receptor complexes for interleukin-6 and leukaemia inhibitory factor. Signal transduction by CNTF requires that it binds first to CNTFR alpha, permitting the recruitment of gp130 and LIFR beta, forming a tripartite receptor complex. CNTF stimulates gene expression, cell survival or differentiation in a variety of neuronal cell types such as sensory, sympathetic, ciliary and motor neurons. CNTF is not essential for neural development, but instead acts in response to injury or other stresses. CNTF exerts a protective effect in demyelinating disease by preventing apoptosis of oligodendrocytes. CNTF also exerts an anti-inflammatory effect on the central nervous system.

In a human study examining its usefulness for the treatment of motor neuron disease, an unexpected weight loss was observed [21]. Further investigation revealed that CNTF mimics the biological actions of leptin while overcoming leptin resistance, and remains effective even after termination of therapy if administered centrally. *Axokine,* a second-generation neurotrophic factor that is related to CNTF with a 15 amino acid truncation of the C terminus and two amino acid substitutions, is three to five times more potent than CNTF in *in vitro* and *in vivo* assays, has improved stability properties and was shown to result in more weight loss than placebo [22]. Studies with Axokine were stopped due to the development of neutralizing antibodies against CNTF in a significant number of patients. There is also the possibility that subjects producing antibodies against CNTF analogues may eventually suffer severe side effects, as these antibodies could potentially interfere with the neuroprotective functions of endogenous CNTF. This strategy as a potential anti-obesity target warrants further investigation [23, 24].

Subtype-Selective Serotonin-Receptor Agonists

Endogenous hypothalamic serotonin (5-HT) plays an important part in within-meal satiation and post-meal satiety processes, apart from in several sensory, motor and behavioural processes. Numerous serotonin receptor subtypes have been identified; of these, serotonin 5-HT2C and 5-HT1B receptors have been specifically recognized as mediators of serotonin-induced satiety [25-27]. The activation of 5-HT2C receptors on arcuate POMC neurons engages the same melanocortin pathway that is critical to leptin-mediated anorexia. 5-HT1B activation on arcuate NPY/Agrp cells inhibits neuronal activity, resulting in indirect stimulation of POMC cells, complementing the direct activation of the same neurons by the 5-HT2C receptor. This effect lies downstream of some of the levels at which leptin resistance occurs in obesity. Thus, the serotonin system has provided a viable target for weight control [28].

A small number of short-term studies using isoform-selective 5-HT agonists confirm that the stimulation of 5-HT2C receptor, and possibly 5-HT1B receptor, reduces food intake and weight in humans. A combined 5-HT2C/1B agonist (m-chlorophenylpiperazine) and the selective 5-HT2C agonist lorcaserin ((1*R*)-8-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine, APD356) have been tested in obese individuals, with modest but significant results. Several 5-HT2C selective agonists are under development [29]. In addition, 5-HT6 receptor antagonists such as PRX-07034 and BVT74316 have been shown to reduce food intake and bodyweight gain in rodent models and have recently entered clinical trials [30-32].

INHIBITION OF OREXIGENIC SIGNALS

Neuropeptide Y Receptor Antagonists

Neuropeptide Y (NPY) is one of the most abundant and widely distributed peptides in the central nervous system of both rodents and humans [33]. It has been implicated in a variety of physiological actions, including control of body weight. In mammals, the signalling is mediated *via* at least five different cell surface receptors, denoted as Y(1), Y(2), Y(4), Y(5) and Y(6). There is no consensus regarding which subtype is the most important for NPY-induced feeding, and attempts to demonstrate an important role for NPY in the control of food intake have produced equivocal results. Antagonists of the NPY Y(1) and NPY Y(5) receptor subtype initially looked promising, since analogues of NPY with high selectivity for these receptors strongly stimulated food intake. However, attempts to inhibit the signalling of NPY through the NPY Y(1) and NPY Y(5) receptors has produced equivocal effects on food intake, and clinical studies of Y-receptor antagonists are almost nonexistent at present. Patients in whom the starvation response is activated, such as formerly obese patients who have lost weight, may be the best candidates for treatment with a neuropeptide Y receptor antagonist.

Melanin-Concentrating Hormone Antagonists

Melanin-concentrating hormone (MCH) is a cyclic, non-adecapeptide abundantly present in mammalian neurons and expressed in brain regions known to be at the centre of feed-

ing behaviour. MCH binds to and activates two G protein-coupled receptors, MCH1R and MCH2R. The MCH-1 receptor (MCH-R1) has been identified as a key target in MCH regulation. In addition to the crucial roles of MCH in feeding behaviour, anatomical and neurochemical studies suggest that the MCH/MCH(1) system is involved in the regulation of emotion and stress responses. Therefore, it is important to develop anti-MCH agents that selectively modulate energy homeostasis without exerting other side effects.

Multiple chemotypes of small molecule MCHr1 antagonists have been identified and shown to induce weight loss in animal models [34-36], but many of these lead compounds have been found to cross-react with the hERG potassium channels (which are involved in cardiac action potential repolarization) and/or demonstrate deleterious effects on cardiovascular haemodynamic parameters. Difficulties in identifying a compound with an acceptable therapeutic index could be attributed to at least two factors: high levels of sustained drug exposure in the brain was required to achieve efficacy, and many small molecule MCHR1 receptor antagonists suffer from receptor cross-reactivity that leads to cardiovascular toxicity at low multiples of their therapeutic plasma concentration.

Somatostatin Analogues

Somatostatin and its analogues (octreotide and lanreotide) bind to somatostatin subtype 5 receptors on the beta-cell membrane, which limits insulin release and, consequently, may decrease adipogenesis. Long-acting release octreotide was used in hyperinsulinaemic obese adults and resulted in statistically significant weight loss [37, 38]. The patients with the highest degree of insulin hypersecretion appeared to derive the most benefit from treatment.

GASTROINTESTINAL PEPTIDES THAT REGULATE FOOD INTAKE, AS DRUG TARGETS

Information about short-term changes in plasma levels of certain nutrients are communicated to the brain through gastrointestinal peptides, acting in conjunction with information about gastric distension, *via* the vagal and spinal nerves [39-41]. Except for ghrelin, gastrointestinal signals contribute to satiation.

As is the case with other potential targets in the development of anti-obesity drugs, one of the greatest problems of gastrointestinal hormone-based therapies is their potential efficacy. Individual peptides are not secreted in isolation in response to nutrient ingestion. Rather, there is a coordinated release of several hormones that act in coordination with CNS reward pathways, input from higher centres and social and environmental influences. This short-acting GI signals are processed in the central nervous system, along with information about the status of the body energy stores, to elicit corresponding alterations in catabolic and anabolic neuropeptides and neurotransmitters to control energy homeostasis. In order to increase the efficacy of anti-obesity drugs, it will probably be necessary to develop combination agents that target multiple signals in the energy homeostasis system.

The theoretical advantage of reproducing the body's own satiety signals would be the minimal disturbance of ubiquitous neurotransmitter systems, and therefore undesirable side effects would be expected to be reduced. Nausea has been one of the most common side effects of experimental treatments with gut peptides as anti-obesity agents. One issue that limits the use of native peptides is their short half-life, which conditions inconvenient administration regimes. The development of stable analogues and novel methods of drug delivery are crucial parts of drug development.

Gastrointestinal peptides that regulate food intake include glucagon-like peptide-1, peptide YY3-36, oxyntomodulin (OXM) and ghrelin, amongst others. Gut hormones as potential new targets for appetite regulation and treatment of obesity have recently been reviewed [42].

Glucagon Like Peptide (GLP-1) Receptor Agonists

Pre-proglucagon derived peptides Glucagon-Like Peptide-1 (GLP-1), Glucagon-Like Peptide-2 (GLP-2) and oxyntomodulin (OXM) are involved in a wide variety of physiological functions. The major physiological role of GLP-1 in mammals is to connect the consumption of nutrients with glucose metabolism [43]. To date, clinical development has focused on its incretin effect (intestinal enhancer of insulin secretion) and its use as anti-diabetic agents. Peripheral administration of GLP-1 derivatives and analogues to both rodents and humans has shown to have effects on food intake and body weight [44-46].

The therapeutic utility of the native GLP-1 molecule is limited by its rapid enzymatic degradation by a serine protease known as dipeptidyl peptidase-IV (DPP-IV). A number of DPP-IV-resistant GLP-1 agonists, including exenatide and liraglutide, have been developed. Exenatide, or exendin-4, ($C_{184}H_{282}N_{50}O_{60}S{\cdot}C_2H_4O_2$), was extracted from the venom of the Gila monster; it is supplied for subcutaneous (SC) injection and marketed to treat diabetes, and causes a modest but progressive weight lost. Liraglutide Arg(34)Lys(26)-(N-epsilon -(gamma-Glu(N-alpha-hexadecanoyl))-GLP-1(7-37) was synthesized using the GLP-1 sequence with the addition of an acyl side chain that allows for noncovalent binding to albumin, which prolongs its half-life in the circulation. In trials evaluating the efficacy of incretin therapy in Type 2 diabetes that reported data on changes in weight, there was a statistically significant weight loss observed with GLP-1 analogues *vs*. comparator groups. Weight loss was less pronounced with liraglutide [47, 48]. Although GLP-1 receptor agonists are not currently approved for obesity treatment, they could have a role as an anti-obesity treatment [49].

Peptide YY Analogues

PYY3–36 is the major form of circulating PYY and binds to the hypothalamic Y2 receptor. PYY is hypothesised to inhibit food intake *via* activation of the auto-inhibitory presynaptic NPY Y2-R present on the ARC NPY neurons, and activating adjacent anorexigenic POMC neurons [50, 51]. The role of oxyntomodulin and peptide tyrosine-tyrosine (PYY) in appetite control has recently been reviewed [52, 53]. It has been suggested that disregulation in the secretion of this anorexigenic peptide may contribute to the complex pathogenesis of anorexia of some diseases, such as chronic renal failure [54]. Effects on other processes affecting energy balance (energy expenditure, fuel partitioning, gut nutrient

uptake) remain poorly understood. Besides energy balance, PYY has been shown to coordinate gastrointestinal functions and has some role in other systemic functions such as controlling blood pressure, heart rate and sleep.

PYY3–36 has a functional half-life of approximately 3 h. The attachment of polyethyleneglycol (PEG) and coupling it to a 40 kDa PEG through a spontaneously cleavable linker develops a reversible PEGylated PYY3–36 derivative, and results in an eightfold increase in its functional half-life, to approximately 24 h. Variability of its effect across different experimental conditions in animal models led to confusion regarding its potential as an anti-obesity treatment. Some studies suggest that PYY has, if at all, only a minor role in food intake in rats, although a number of groups have demonstrated that peripheral PYY3-36 inhibits food intake and reduces body weight gain in other species. The pattern of administration is critical for producing a sustained effect of PYY3–36 on food intake and adiposity in rodents.

Obese human subjects have reduced basal and meal-stimulated release of total PYY, consistent with a secreting defect. Intravenous PYY3–36 infusion into humans induces satiety and reduces food intake [55, 56], without eliciting illness or subsequent compensatory hyperphagia, although the inhibition appears only significant at high physiological or pharmacological plasma concentrations. In one study, intranasal PYY(3-36), at the doses administered and with preprandial timing, was not efficacious in inducing weight loss in obese patients [57]. The injectable PYY3–36 analogue AC-162352 was tested in phase I studies, with limited success due to nausea.

In conclusion, the pharmacological value of PYY is controversial. Further studies are indicated to determine the potential role in energy balance regulation, and the optimal delivery and dosing.

Ghrelin Receptor Antagonists and Inverse Agonists

Ghrelin is the only known gut orexigenic hormone. It is an endogenous ligand for GH secretagogue 1A receptor (GHS_{1A}-R). Apart from other actions, it seems to have a role in meal initiation and long-term control of body weight [8]. We have studied the potential relationships between ghrelin and malnutrition in some chronic diseases [58, 59]. Ghrelin levels are low in obese individuals and rise in response to weight loss, as a compensatory response to promote weight regain. This could suggest that disruption of ghrelin signalling would not be useful in treating obesity. Several factors indicate that this idea may be incorrect: it is possible that obese individuals are more sensitive to the orexigenic effects of ghrelin [60] and obesity is associated with an attenuation of the post-prandial ghrelin decrease [61]. It is also possible that ghrelin blockage would be more useful in preventing weight regain, after weight loss is achieved by other means.

Highly potent GHS_{1A}-R antagonists have been identified [62-65]. In rat models, some but not all GHS_{1A}-R antagonists decreased food intake and body weight when administered centrally or intraperitoneally [66, 67]. The GHS_{1A}-R has constitutive activity [68] and, therefore, inverse GHS_{1A}-R agonists [69] may prove to be more effective in inducing weight loss than GHS_{1A}-R antagonists. Other more innovating approaches to decrease ghrelin activity have also been investigated as potential anti-obesity treatments [70-73].

Oxyntomodulin Analogues

Oxyntomodulin is a 37-amino-acid peptide that contains the 29-amino-acid structure of glucagon, followed by an octapeptide C-terminal extension [74]. The existence of a separate oxyntomodulin receptor has not been clearly demonstrated. It has been suggested that oxyntomodulin exerts its anorectic effect by signalling through the GLP-1 receptor. The administration of oxyntomodulin, when given intraperitoneally or into the cerebral ventricles, has been observed to reduce short-term food intake in rodents [75, 76]. Oxyntomodulin-treated animals lose more weight than control animals that consume the same amount of calories, which suggests that oxyntomodulin increases energy expenditure, possibly *via* an effect on the thyroid axis. Oxyntomodulin has been found to reduce energy intake in normal-weight volunteers when administered intravenously or subcutaneously before a single study meal [77-79]. This weight-loss effect in humans could be caused by an increase in energy expenditure, in addition to a decrease in energy intake, as previously suggested by rodent data. Nausea has been reported associated with very high plasma levels of oxyntomodulin after exogenous administration.

DRUGS THAT INCREASE ENERGY EXPENDITURE

β3-adrenergic agonists cause lipolysis and increase thermogenesis. Their main sites of action are white and brown adipose tissue, and muscle. All weight loss is lipid and lean may actually increase, so reducing weight loss relative to energy loss. *β3-adrenoceptor agonists* fall into two main chemical classes: arylethanolamines and aryloxypropanolamines. It is difficult to identify β3-adrenoceptor agonist drugs because of differences in pharmacology between the rodent and human *β3*-adrenoceptors [80, 81]. Moreover, near absolute selectivity is needed to avoid β(1/2)-adrenoceptor-mediated side effects, and selective agonists tend to have poor oral bioavailability. Several phase II trials with this type of drugs were discontinued because of poor drug efficacy [82, 83] and safety profiles.

Human growth hormone (GH) has profound lipolytic/antilipogenic actions *in vivo* and its secretion is decreased in obesity [84, 85]. Recently a meta-analysis of human studies examining the efficacy and safety of recombinant GH as therapy for obesity in adults was carried out [86]. It was concluded that rhGH therapy leads to a decrease in visceral adiposity and an increase in lean body mass as well as beneficial changes in lipid profile in obese adults, without inducing weight loss. rhGH treatment was associated with increases in fasting plasma glucose and insulinemia. The rhGH doses used in many studies were supraphysiological, and the authors suggested that future studies of longer duration, using carefully titrated rhGH protocols, will be needed in order to fully establish the effects of rhGH therapy in obesity. Growth hormone receptor agonists could be another potential target for obesity treatment. A small region of the growth hormone molecule, denoted hGH 177-191, appears to retain some of the actions of growth hormone, but with no effect on growth or on insulin resistance. An orally active peptide variant of hGH 177-191, called AOD9604, was revealed to

stimulate fat metabolism in animal trials [87, 88]. After a phase IIB clinical trial of 407 subjects was completed in 2006, the company concluded that the results did not support the commercial viability of the drug as a treatment for obesity.

COMBINATION THERAPY APPROACHES

The efficacy limitations of current single-target drugs, and the possibility for counter-regulatory responses that may compensate, adapt or influence the homeostatic system during drug- induced weight loss, provides a framework for the discovery and development of combination agents that target multiple signals in energy homeostasis. Approaches may involve low-dose multiple drug combination and/or peripheral and centrally acting combinations.

CONCLUSION

Obesity and overweight are highly prevalent chronic conditions that are associated with premature mortality, chronic morbidity and increased healthcare use. At present, available pharmacotherapy options remain very limited, and approved anti-obesity therapies promote small mean weight losses. The development of new and more effective drugs has become a research priority

The three potential strategies to achieve weight loss are: 1) to reduce energy intake, by stimulating anorexigenic signals or by blocking orexigenic signals, and 2) to increase energy expenditure. All these strategies are being actively investigated, although it is not likely that a solution will be available in the near future. The desired degree of effectiveness will more probably be achieved through the use of combinations of treatments.

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