New central targets for the treatment of obesity

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The review focuses on the central neuronal circuits involved in energy homeostasis and the opportunities these offer for pharmacological intervention to decrease feeding behaviour and reduce weight. This article is based on the presentation '*New central targets for the treatment of obesity*' (Sargent, British Pharmacological society, Clinical Section Symposium, December 2008). Central neuronal substrates controlling weight offer numerous opportunities for pharmacological intervention. These opportunities range from non-specific enhancement of monoamine signalling (triple reuptake inhibitors) to targeting specific monoamine receptor subtypes (5-HT_{2c} and 5-HT_6). The data reviewed suggest that these approaches will lead to weight loss; whether this is sufficient to produce clinically meaningful effect remains to be determined. Combination therapy targeting more than one mechanism may be a means of increasing the magnitude of the response. Preclinical studies also suggest that novel approaches targeting specific neuronal pathways within the hypothalamus, e.g. MCH_1 receptor antagonism, offer an opportunity for weight reduction. However, these approaches are at an early stage and clinical studies will be needed to determine if these novel approaches lead to clinically meaningful weight loss and improvements in co-morbid conditions such as diabetes and cardiovascular disorders.

The obesity problem

Obesity is a major global health problem and rates of obesity [body mass index (BMI) $>30 \text{ kg m}^{-2}$] have risen steadily year on year. Recent figures show an incidence of obesity of more than 1 in 4 in many parts of the USA [1]. These high rates are similar in other developed countries and the incidence of weight gain is increasing in less developed regions. Obesity is not just a cosmetic or lifestyle illness but leads to many life-threatening health complications. As the BMI increases the incidence of metabolic disorders (Type 2 diabetes), hypertension, cancer and musculoskeletal problems increases [1–3]. In 1999, Calle *et al.* reported mortality rates for all causes doubled when the BMI increased from 25 to >35 [4]. The annual direct health-care costs associated with obesity in the USA are in excess of $93 billion [5]. Particularly worrying is the fact that the incidence of obesity in children and young adults is on the increase, with some reports suggesting that up to 25% of children may be obese. The long-term health implications of these findings are far reaching and suggest that for the first time intergenerational increase in life expectancy will not occur and these children will have a shorter life span than their parents because of health complications associated with weight gain [6] (Figure 1).

Obesity occurs when the balance between energy input (food intake) and energy expenditure (exercise, activity) is disrupted, i.e. more food is consumed than utilized, leading to excess fat stores being laid down. Although for some people a calorie-restricted diet and exercise can lead to a reduction in weight gain, for many people this is not enough and weight loss cannot be maintained. There are many environmental factors that predispose individuals to gain weight, e.g. freely available high-calorie food and sedentary life style [7]. Genetic factors also contribute to this imbalance; for example, the 'Thrifty-gene' hypothesis proposes that humans particularly prone to famine have evolved to favour the storage of excess calories in the form of fat [7]. In the severely obese, surgical intervention may be necessary (see review in this supplement). An alternative approach is to develop therapeutic agents that can either reduce food consumption or increase energy utilization.

This review is based on the presentation 'New central targets for the treatment of obesity' (Sargent, British Pharmacological society, Clinical Section Symposium

Men
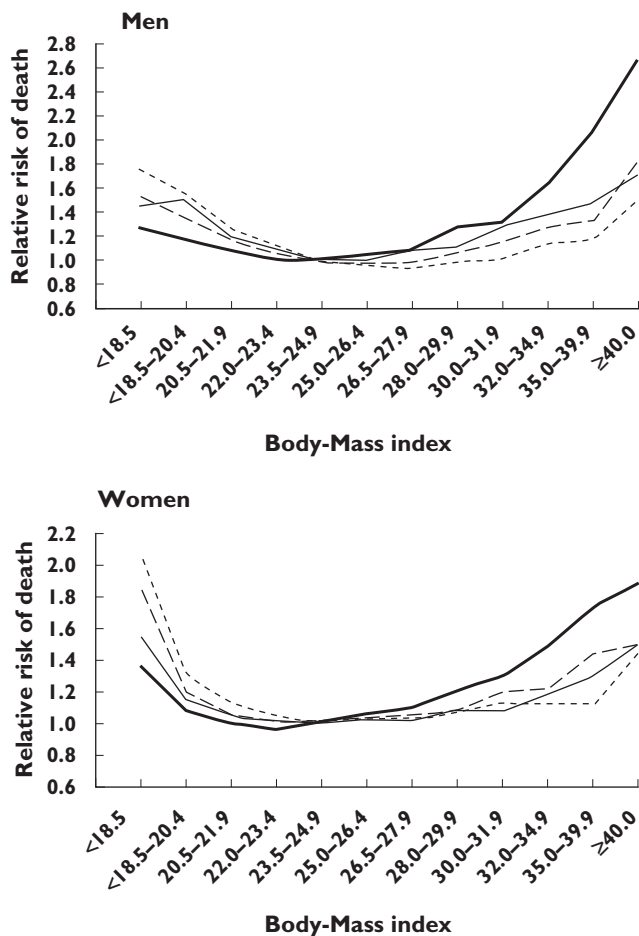
Women

Figure 1

Multivariate relative risk of death from all causes among men and women according to body mass index, smoking status, and disease status. The four subgroups are mutually exclusive. Nonsmokers had never smoked. The reference category was made up of subjects with a body mass index of 23.5–24.9. Calle *et al*. N Engl J Med 1999; 341: 1097–105. Current or former smokers with a history of disease (----); Current or former smokers with on history of disease (– –); Nonsmokers with a history of disease (—); Nonsmokers with no history of disease (▬)

December 2008) and focuses on central neuronal circuits involved in energy homeostasis and the opportunities these offer for pharmacological intervention to reduce feeding behaviour and reduce weight gain. The review is not intended as an in-depth analysis of each individual mechanism, but will highlight the breadth of approaches and direct readers to other recent reviews and articles that address these approaches in much more detail.

## Hypothalamus and the central control of feeding and energy homeostasis

The hypothalamus is the key processing area within the brain for the integration of numerous signals related to energy homeostasis. Peripheral signals of satiety are inte-

grated and passed on to other areas of the brain via nuclei in the hypothalamus. All agents that act to reduce food intake and weight gain will directly or indirectly influence activity within the hypothalamus. Peripheral signals from adipose stores, the gastrointestinal tract and endocrine system influence the activity of neurons within the arcuate nucleus of the hypothalamus. When fat stores are reduced and energy levels are low, hunger signals mediated via an increase in the gut hormone, ghrelin, and reductions in insulin, glucose, leptin and cholecystokinin (CCK) cause increases in the activity of both neuropeptide Y (NPY) and agouti-related protein (AgRP) neurons, which in turn leads to decreased activity of the melanocortin system, leading to disinhibition of melanin-concentrating hormone (MCH) and orexin (ORX) signalling producing a marked orexigenic effect. Following a meal the reverse occurs, with high levels of glucose, insulin, CCK and reduced ghrelin levels leading to increases in pro-opiomelanocortin (POMC) and cocaine-amphetamine regulated transcript (CART) neuronal activity, in turn increasing α-melanocyte-stimulating hormone (α-MSH) release and decreasing MCH/ORX activity, leading to satiation and a termination of feeding (Figure 2) [8–21].

Centrally acting pharmacological treatments of obesity

A number of central agents have been developed for the treatment of obesity [21, 22]. These agents produced their actions through the modification of biogenic amine function [17, 23]. The first agents used were amphetamine-like compounds, and although they produced significant weight loss, the stimulant properties and abuse liability led to their demise. Analogues that did not have the dopamine reuptake/releasing properties were subsequently developed, culminating in the development of the serotonin releaser, d-fenfluramine and the sympathomimetic, phentermine. These compounds, particularly when used in combination (fen/phen) produced significant weight loss. d-Fenfluramine produces its action via the release of 5-HT plus direct stimulation of 5-HT$_{2C}$ receptors located in the hypothalamus. The increase in serotonin within the hypothalamus activates POMC neurons, via the 5-HT$_{2C}$ receptor. The POMC neurons play a key role in the regulation of feeding by sending anorectic signals to the periventricular nucleus (PVN) and other brain areas associated with energy homeostasis. Fenfluramine and the fen/phen combination were withdrawn following a number of cases of pulmonary hypertension and cardiac valvulopathy [17, 21].

One compound, acting via monoamine reuptake inhibition, currently marketed is sibutramine (Table 1). Sibutramine is a serotonin/noradrenaline reuptake inhibitor that produces robust weight loss in rodent models of obesity. Sibutramine acts by increasing noradrenaline and serotonin levels in the hypothalamus, nucleus accumbens and the brainstem, all regions associated with energy homeostasis [23]. The desmethyl metabolites of sibutramine have signifi-
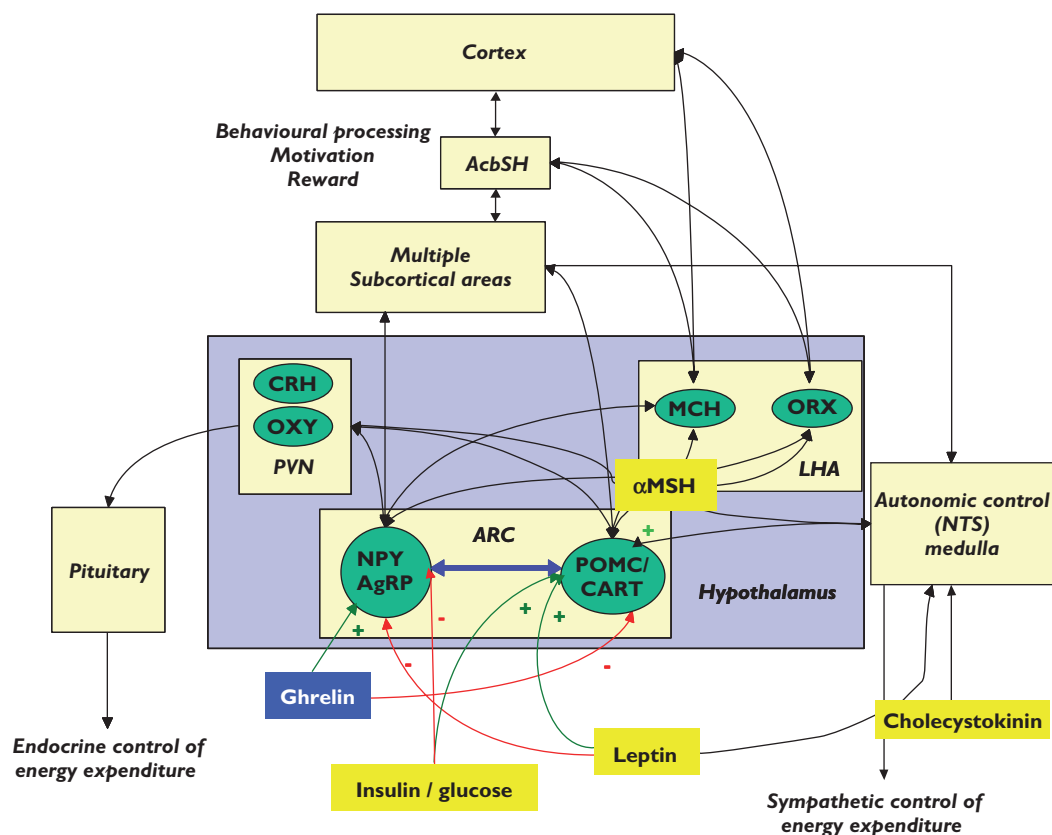
Figure 2

Circuits implicated in the central control of feeding. AcbSH, nucleus accumbens shell; AgRP, agouti gene-related peptide; ARC, arcuate nucleus; CART, cocaine-amphetamine regulated transcript; CCK, cholecystokinin; CRH, corticotrophin releasing hormone; LHA, lateral hypothalamus; α-MSH, alpha-melanocyte stimulating hormone; MCH, melanin-concentrating hormone; MC4R, melanocortin 4 receptor; NPY, neuropeptide Y; NTS, tractus solitari; ORX-orexin (hypocretin); OXY, oxytocin; POMC, pro-opiomelanocortin; PVN, periventricular nucleus

Table 1

Centrally acting marketed or compounds in clinical development for the treatment of obesity

Company	Product name/code	Product type	Phase
Abbott	Sibutramine	NA/5HT reuptake inhibitor	Authorized
Arena Pharma	Lorcaserin	$5HT_{2C}$ agonist	Phase III
Athersys	ATHX-105	$5HT_{2C}$ agonist	Phase I
Biovitrum	BVT.74316	$5HT_6$ antagonist	Phase I
Dov Pharmaceuticals	Dov 21947	NA/DA/5HT reuptake inhibitor	Phase II
EPIX Pharma	PRX-07034	$5HT_6$ antagonist	Phase I
NeuroSearch	Tesofensine	NA/DA/5HT reuptake inhibitor	Phase II
Orexigen	Contrave	Bupropion + naltrexone	Phase III
Orexigen	Empatic	Bupropion + zonisamide	Phase II
Shionogi	S-2367	Neuropeptide Y5 inhibitor	Phase II
Vivus	Qnexa	Phentermine + topiramate	Phase II

cant dopamine reuptake inhibition, and this may contribute to the overall profile of the compound *in vivo* [24, 25]

In the clinic, sibutramine causes weight loss, of about 4% compared with placebo, over the course of 12–18 months. Sibutramine also increased the percentage of patients achieving at least a 5 or 10% weight reduction. Sibutramine-induced weight loss was also accompanied by a significant reduction in high-density lipoprotein-cholesterol and triglycerides, but raised heart rate and blood pressure [26].

A recent report has questioned the utility of currently available antiobesity agents on both an efficacy and cost basis. In the survey, payers stated a threshold of about 18% weight loss from placebo would influence formulary coverage and reimbursement [27].

It is clear that additional compounds with superior efficacy and improved safety are required.

New pharmacological approaches to the regulation of food intake and weight loss

Monoamine reuptake inhibitors Monoamine regulation of food intake remains an area of great interest. Astrup *et al*. recently reported Phase II clinical data on tesofensine. Tesofensine is a triple reuptake inhibitor that blocks the reuptake of noradrenaline, serotonin and dopamine [28]. Tesofensine, combined with diet, produced approximately a 10% (12.8 kg) reduction in weight at the highest dose tested (1 mg) compared with a 2% (2.2 kg) weight loss in the placebo group. However, this dose was also associated with a significant increase in heart rate and blood pressure. Lower doses (0.25–0.5 mg) produced a 4.5–9% decrease in body weight with no associated change in blood pressure. A slight tachycardia was noted with the 0.5-mg dose. Dov Pharmaceuticals are also developing a compound that acts by inhibiting the reuptake of dopamine, serotonin and noradrenaline. Dov 21947 at doses up to 150 mg has been reported to produce a significant decrease in body weight of 2.1 kg compared with the placebo group in an 8-week study [29].

5-HT$_{2C}$ agonists as potential obesity treatments

Studies using serotonin reuptake inhibitors and selective serotonin agonists and antagonists have clearly implicated serotonin in the regulation of feeding and energy homeostasis. Studies in animals using both transgenic knock-out animals and selective agonists show that stimulation of the 5-HT$_{2C}$ receptor decreases food intake and body weight in both lean and obese rodents. Stimulation of 5-HT$_{2C}$ receptors has been implicated in the hypophagic action of fenfluramine. Many 5-HT$_{2C}$ agonists have been developed over the years; however, selectivity over other 5-HT$_2$ receptors has remained a major challenge. Stimulation of 5-HT$_{2C}$ receptors produces a hypophagic effect and blockade of the 5-HT$_{2C}$ receptor has been implicated in drug-induced weight gain [30]. Stimulation of 5-HT$_{2A}$ receptors produces unwanted hallucinogenic-like effects and activity at the 5-HT$_{2B}$ receptor implicated in valvulopathy and pulmonary hypertension limiting the use of relatively nonselective agents [21].

5-HT$_{2C}$ agonists are thought to exert their hypophagic actions via stimulation of receptors located on POMC containing neurons within the arcuate (ARC) nucleus. Recent transgenic data add support to the proposal that 5-HT$_{2C}$ receptors on POMC neurons play a crucial role in the regulation of feeding. Mice lacking the 5-HT$_{2C}$ receptor developed hyperphagia and weight gain and showed an attenuated response to the anorexigenic 5-HT$_{2C}$ agonist, 1-(m-chlorophenyl)piperazine (mCPP). Selective re-introduction of 5-HT$_{2C}$ receptors on POMC containing neurons reversed the KO-induced deficits and normalized both feeding and weight gain [30–33].

Lorcaserin (ADP359) is a selective 5-HT$_{2C}$ agonist currently in clinical development for obesity. In a Phase II study subjects with a BMI = 30–45 received lorcaserin (10 mg q.d., 15 mg q.d. or 10 mg b.i.d.) for 12 weeks. Lorcaserin produced a dose-related increase in the number of patients displaying a >5% weight loss. For example, only 2.3% of patients on placebo demonstrated >5% weight loss, whereas 31% of patients receiving 10 mg b.i.d. showed >5% weight loss. Fasting blood sugar, cholesterol and waist circumference were also reduced. Adverse events were modest and no increased incidence of valvulopathy or pulmonary hypertension was noted [34].

5-HT$_6$ antagonists as potential obesity targets

The 5-HT$_6$ receptor has recently attracted attention as a potential target for the treatment of obesity [35]. 5-HT$_6$ KO animals demonstrated a resistance to weight gain when placed on a high-fat diet. In another series of experiments, it was found that antisense oligonucleotides directed at the 5-HT$_6$ receptor decreased body weight and food intake in rats. Woolley *et al*. [36] also observed that a high dose of the 5-HT$_6$ antagonist Ro 04-6790 significantly attenuated body weight gain in growing rats when administered for 3 days. Since these original studies, a number of others have reported reductions in food intake following 5-HT$_6$ antagonist administration [37]. The exact mechanism of 5-HT$_6$-mediated reductions in food intake is unclear. However, 5-HT$_6$ receptor mRNA is found in the ARC and it has been proposed that the blockade of 5-HT$_6$ receptors reduces GABAergic inhibitory control of POMC neurons and the subsequent increase in the release of α-MSH and stimulation of MC-4 receptors leading to a reduction in food intake [35].

It should be noted that in most cases relatively high doses of 5-HT$_6$ antagonists are required to influence food intake compared with doses efficacious in cognition models. This may suggest that the overall effect on food intake is mediated via 5-HT$_6$ antagonism plus additional actions.

Cannabinoid antagonists as antiobesity agents

There is substantial evidence that endocannabinoids are involved in the control of appetite and body weight, and

these effects appear to be mediated via the CB_1 receptor [38, 39]. Tetrahydrocannabinol and cannabis both increase high fat and highly palatable diet intake. The endogenous cannabinoid anandamide has also been shown to increase food intake when injected into the brain, while CB_1 KO mice show reduced food intake and weight gain. The highly selective CB_1 antagonist rimonobant inhibits intake of palatable foods by marmosets and reduces intake of high-fat diet in rodents. However, rimonobant has no effect on normal laboratory chow intake. Pair feeding studies also show that the weight loss produced by CB_1 antagonists is greater than that predicted based on reduction in calories consumed alone, suggesting that CB_1 antagonists increase energy expenditure in addition to reducing food intake [21, 40].

The central actions of endocannabinoids on food intake are mediated by direct action within the hypothalamus. Endocannabinoids are under negative control by leptin, the adipocyte hormone that inhibits orexigenic signalling in the hypothalamus. In genetically obese animals that have disrupted leptin function, the endocannabinoids system is found to be overactive. Activation of CB_1 receptors within the hypothalamus results in the disinhibition of MCH release, producing an orexigenic action [21].

Rimonobant and a number of other CB_1 antagonists (taranabant, otenabant, surinabant and ibipinabant) have been taken into clinical development and shown to produce significant decreases in body weight. In a recent meta-analysis, rimonobant was shown to produce a 4.7-kg reduction in body weight after 1 year, an effect size similar to that observed for sibutramine. Rimonobant also significantly reduced placebo subtracted waist circumference, blood pressure and triglyceride concentrations [41]. The CB_1 antagonist significantly increased the incidence of psychiatric adverse events (notably, depression, anxiety, irritability and aggression). These adverse events led to the withdrawal of rimonobant and termination of the development of several other CB_1 antagonists for obesity [42].

Combination pharmacotherapy as an alternative approach

Clinical experience with existing treatments suggests that weight loss produced by any one agent is limited and rarely exceeds 10% of the starting weight. This initial drop also plateaus. The 'ceiling effect' observed is probably due to adaptive changes as the body continues to maintain a balance in favour of energy conservation. One approach that some have adopted to overcome this issue is to develop combination therapies that tackle the problem through more than one mechanism, thus minimizing the impact of adaptive changes.

The noradrenaline/dopamine reuptake inhibitor, bupropion, when combined with the opiate antagonist naltrexone, has been reported to produce a significant loss of 9.3–11.5% of baseline body weight in a recent the Phase III trial. Twice as many subjects lost $\geq$10% weight compared with the placebo group. The mechanism of action of the bupropion/naltrexone combinations is thought to be through the dual action of monoamine elevation enhancing POMC neuronal activation accompanied by a blockade of the natural endorphin negative feedback that inhibits α-MSH release [43]. Bupropion has also been combined with zonisamide, the anticonvulsant compound, to augment the bupropion-induced weight loss [43].

Another combination therapy in development is phentermine and the anticonvulsant, topiramate (Qnexa). In a Phase II trial, the combination treatment produced significantly more weight loss than either compound alone. In a recently reported Phase III study, the percentage of patients achieving >10% loss was 66% for the combination treatment compared with 7% in the placebo group. Additional analysis showed a significant control of blood sugar in these nondiabetic subjects compared with the placebo group. Subjects receiving active treatment had a significant improvement in glycaemic control as measured by a reduction in haemoglobin A_{1c} compared with placebo [44].

Direct modulation on neuropeptide transmitters within the hypothalamus

Within the hypothalamus, a number of peptide transmitters are involved in the integration of peripheral satiation and hunger signals and have either orexigenic or anorexigenic effects. Pharmacological manipulation of these targets offers another approach to regulating food intake [11].

Neuropeptide Y antagonists

NPY is a 36 amino acid neurotransmitter widely distributed within the brain. The arcuate nucleus has a large concentration of NPY-containing neurons that then innervate the PVN and lateral hypothalamus. NPY actions are mediated via multiple receptors (NPY_{1-6}). Studies using the peptide have shown that administration of NPY produces marked stimulation of feeding and energy expenditure by activating NPY_1 and $_5$ receptors within the hypothalamus [45, 46]. NPY levels are regulated by leptin and other peripheral modulators (e.g. gut hormones); following a meal when leptin levels are low, NPY activity is reduced [47]. Conversely, NPY levels are elevated during hunger and energy depletion [21]. Selective NPY antagonists, particularly targeting NPY_5 receptors, inhibit feeding and reduce body weight in models of obesity [46]. The Y_5 antagonist MK0557 was recently shown to induce only modest weight loss (3.4 kg) compared with placebo (1.8 kg) in a 52-week study. These results led the authors to conclude that Y_5 receptor activation is involved in energy homeostasis in man; however,

selective blockade of this receptor alone was insufficient to produce clinically meaningful weight loss [47].

Shionogi recently reported positive effects of their NPY_5 antagonist, S-2367, in a Phase IIa proof of concept study. The safety and efficacy of S-2367 was assessed following once-daily treatment in a population of 342 obese subjects. Over the 12-week treatment period, subjects in the high-dose group of S-2367 lost an average of 5.3 kg over 16 weeks, or 5.6% of baseline weight, *vs.* 2.5 kg or 2.7% of baseline weight for placebo. In addition, there was also a clear dose–response between the 400 mg day^{-1} and 1600 mg day^{-1} dosing groups. S-2367 was well tolerated, and no significant or serious safety adverse events occurred [48]. Further long-term studies will be necessary to establish if this weight reduction is clinically relevant.

Melanocortin MC-4 receptor agonists

Decreased activity of the melanocortin system is associated with hunger and the initiation of feeding. α-MSH released by POMC neurons acts on MC_4 receptors to exert an inhibitory effect on the secondary 'leptin-sensitive' MCH and ORX pathways. Injections of MC_4 agonists decrease food intake, whereas inhibition of MC_4 receptor activity by infusion of an MC receptor antagonist or with the inverse agonist AgRP results in increased food intake. MC_4 activity affects meal size and meal choice, but not meal frequency. The type of diet also affects the efficacy of MC_4 agonists to reduce food intake in rats [15, 49, 50].

Mutations in the human melanocortin MC_4 receptor have been associated with obesity, which underscores the relevance of this receptor as a drug target to treat obesity. A number of groups have looked at the development of selective agonists for MC_4 as potential treatments for obesity. However, the lack of suitable small-molecular-weight nonpeptide agonist ligands or adverse events have limited clinical development of this target [15, 49, 50].

Melanin concentrating hormone antagonists

ARC NPY-AgRP and POMC neurons project to brain regions involved in energy homeostasis, including the PVN, LHA and nucleus accumbens shell. These so-called 'leptin-sensitive' neurons express significant amounts of MCH. MCH has been identified as an orexigenic peptide that exerts an effect on food intake and body weight regulation [51, 52]. MCH is a cyclic 19 amino acid neuropeptide expressed in the lateral hypothalamus in response to both energy restriction and leptin deficiency. MCH is known to stimulate feeding when injected into the lateral ventricle of rats, and the mRNA for MCH is upregulated in the hypothalamus of genetically obese mice (ob/ob) and in fasted

control animals. In addition, animals treated with MCH show increases in glucose, insulin and leptin levels, mimicking human metabolic syndrome. Mice lacking MCH receptors are hypophagic and lean with increased metabolic rate, whereas animals overexpressing MCH gain excess weight on both standard and high-fat diets. MCH exerts an orexigenic effects via activation of MCH_1 receptors. Indeed, a variety of small-molecule, MCH_1 antagonists have been shown to produce significant weight loss in mouse and rat models of obesity. These compounds have been shown to produce weight loss by reducing meal size [53, 54].

Despite the discovery and preclinical development of many selective MCH_1 receptor antagonists, very few have entered clinical development. One of the main reasons for the lack of clinical development has been the propensity for selective agents to have significant cardiovascular liabilities. Many of the early compounds displayed significant human ether-a-go-go-related gene-binding activity and drug-induced QTc prolongation [52].

Despite the significant challenges encountered by many groups, MCH_1 receptor antagonism remains a very attractive target for obesity. Recently a number of compounds have been reported that possess significant MCH_1 antagonist activity and cause marked weight loss in animals, without producing changes in cardiovascular function associated with other, older MCH_1 antagonists. For example, AMR-MCH-1 was found to bind to the human MCH_1 receptor with a K_i value of 2.6 nM and demonstrated significant and sustained reductions in food intake and body weight in a chronic, 28-day feeding study in male dietary-induced obese C57BL/6J mice. At 30 mg kg^{-1} and 60 mg kg^{-1} (po b.i.d.), AMR-MCH-1 produced weight losses of 11.1% and 13.9%, respectively, compared with 5.8% for positive control sibutramine (20 mg kg^{-1} po q.d.). Fat pad analysis indicated that the weight loss caused by AMR-MCH-1 was associated with reductions in fat mass of 27.5% and 44.6% compared with vehicle. These data indicate that AMR-MCH-1 is a high-affinity MCH_1 receptor antagonist that causes sustained weight loss [55].

Another MCH_1 antagonist, NGD-4715, entered Phase I clinical testing; the initial phase of the multiple ascending dose (MAD) study utilized three times per day dosing for 14 days in healthy obese subjects exposed to a high caloric diet. During the initial phase of this MAD study, induction of the liver enzyme CYP 3A4 occurred and a lipid-lowering effect was also observed. A follow-up study designed to test twice per day dosing in healthy obese subjects on a restricted caloric diet for 14 days was also conducted. Using b.i.d. dosing, CYP3A4 induction was substantially reduced. With less frequent dosing and caloric restriction, no effect on lipids was observed. As in the first Phase I study, no serious adverse events were observed. However, vivid dreams and awakenings were reported by half the drug-treated subjects during the first week of dosing. Development of this compound has subsequently been terminated [56].

Conclusions

Central neuronal substrates of feeding and energy balance offer numerous opportunities for pharmacological intervention. These opportunities range from nonspecific enhancement of monoamine signalling (triple reuptake inhibitors) to targeting specific monoamine receptor subtypes (5-HT_{2c} and 5-HT_6). To date, the evidence shows that these approaches may lead to statistically significant weight loss, but whether this is sufficient to produce clinically meaningful weight reduction remains to be determined. Combination therapy targeting more than one pathway/mechanism may be a means of increasing the magnitude of the response.

Based on animal data, novel approaches targeting specific neuronal pathways within the hypothalamus, e.g. MCH_1 receptor antagonism, offer an opportunity for weight reduction. However, these approaches are at an early stage and clinical studies will be needed to determine if these novel approaches lead to clinically meaningful weight loss and improvements in comorbid conditions such as diabetes and cardiovascular disorders.

Competing interests

None to declare.

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