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Meeting Report

Obesity and its treatment

Highlights of the Society for Medicines Research Symposium

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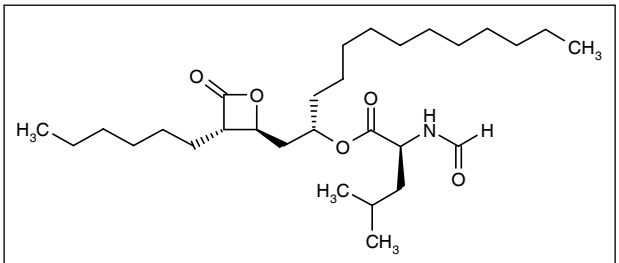
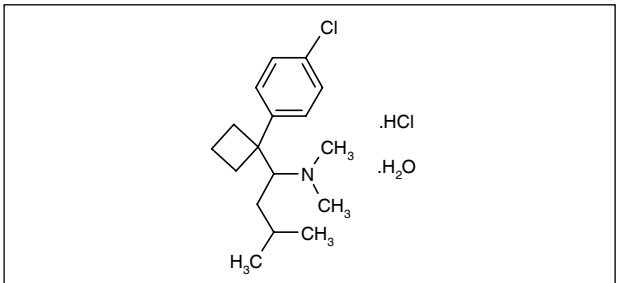
Abstract

The latest global figures from the World Health Organization (WHO) from 2005 indicate that approximately 1.6 billion adults are overweight and at least 400 million are obese, i.e., have a body mass index (BMI = weight/height^2) in excess of 30. By 2015, these figures are projected to rise to 2.3 billion (one-third of the world population) and more than 700 million, respectively. This rise in incidence is underpinned by marked changes in diet and lifestyle in developing countries, along with a continued increase in the number of obese people in Western countries. The healthcare consequences are enormous, particularly as obesity is a major risk factor for cardiovascular disease, diabetes, osteoarthritis and some cancers. This one-day meeting, held on September 25, 2008 in London (U.K.), reviewed the current status of the disorder and explored future prospects for safe and effective pharmacotherapy.

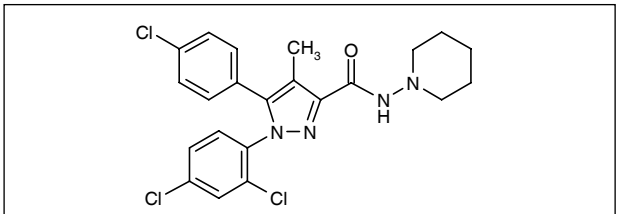
Jon Arch (Clore Laboratories, University of Buckingham, U.K.) opened the symposium with a presentation entitled "Drug Discovery Strategies: Small Steps or Giant Leaps?" Dr. Arch's talk provided the audience with an overview of currently approved drugs for the treatment of obesity, drugs currently in late-stage development and strategic approaches to finding new improved therapeutics. There are currently three drugs approved for the treatment of obesity – **orlistat** (a pancreatic lipase inhibitor), **sibutramine** (an inhibitor of the uptake of both serotonin [5-HT] and norepinephrine [NE]) and **rimonabant** (a cannabinoid CB_1 receptor antagonist). Notably, there have been a number of late-stage clinical failures and market withdrawals in the obesity area, many of which have been due to safety-related issues. Both the FDA and the EMEA have released guideline documents in the last couple of years setting out their requirements for approval of new antiobesity drugs. The guidelines specify requirements in terms of weight loss and lack of weight regain, suggest trials of at least 12 months' duration, seek evidence for favorable effects on metabolic parameters, and require a lack of significant side effects (with particular concern for adverse effects on the cardiovascular and central nervous systems). The three currently approved drugs clearly do not meet all of these criteria. Weight loss seen with these agents is modest (particularly with orlistat) and there is no selectivity for visceral fat reduction. There is little evidence for any effect of orlistat or sibutramine on metabolic parameters over and above effects that would



Orlistat



Sibutramine



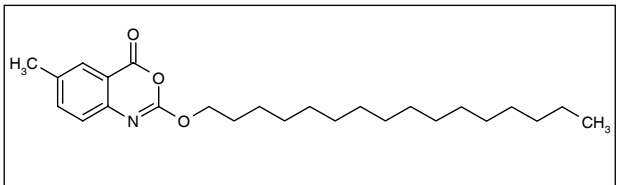
Rimonabant

be associated with diet- or exercise-induced weight loss. Rimonabant does, however, show favorable effects on lipid and glucose levels that appear to be independent of weight loss. These effects of rimonabant appear to be due to the ability of this drug to stimulate fat oxidation and sensitize tissues to insulin (1). In terms of side effects, sibutramine can increase blood pressure and rimonabant has CNS side effects to the extent that this compound has not been approved by the FDA.

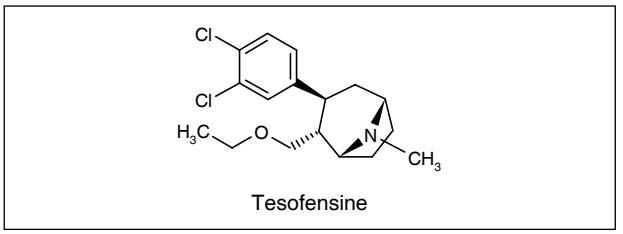
Compounds currently in late-stage development appear to offer only incremental advantages over orlistat, sibutramine and rimonabant. **Cetilistat**, a follow-up molecule to orlistat, appears to have less of a problem with anal leakage, which has been attributed to different effects on micelle formation to those seen with orlistat. **PSN-602** from Prosidion is an inhibitor of 5-HT and NE uptake that also has 5-HT_{1A} receptor-agonist activity, which is reported to prevent increases in heart rate or blood pressure. **Tesofensine** (NeuroSearch) is a 5-HT, NE and dopamine (DA) reuptake inhibitor that has shown good effects on weight loss in phase II trials. Two companies are investigating combinations of existing drugs. Orexigen Therapeutics is evaluating bupropion with either zonisamide or naltrexone, and Vivus is investigating phentermine and topiramate. Effects on weight loss have been reported with these combinations, but questions remain regarding their side effect profiles. Also in late-stage clinical trials are **otenabant hydrochloride** (CP-945598), a CB_1 receptor antagonist from Pfizer, and **lorcaserin**, a 5-HT_{2C} receptor agonist from Arena (see below). There are numerous discovery and development programs being undertaken by the industry, targeting a wide range of mechanisms controlling energy balance. None of the current approaches targeting the CNS, gut hormones or metabolic pathways provide much evidence that a giant leap forward is on the horizon.

David Morgan (AstraZeneca, U.K.) described investigations of the predictive power of rodent models of obesity. He noted that during the evolution of species it has been starvation, rather than obesity, which has applied the greatest selection pressure, and thus diet-induced obesity is easy to induce in many species. Overconsumption of energy-rich diets leads to increased adiposity and body weight in most species. However, while many animals get equally fat, not all fat animals are equal. When choosing from the many obesity models as translational models for the discovery of novel obesity treatments, it is important to bear in mind a number of clinically important considerations: 1) what causes the animals to become obese?; and 2) what is the impact of obesity on the physiology of those animals?

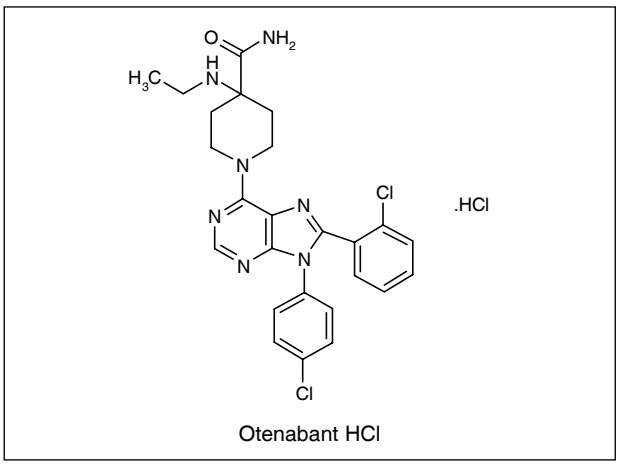
The difference in size between humans and rodents has an important impact on energy balance, with implications for testing drug mechanisms. With regard to feeding patterns, rodents do not exhibit “meal feeding” as humans would, but feed on a more constant basis. These differences in food intake patterns between the species are reflected in differences in how the levels of feeding hormones vary throughout the day. Rodents also have small



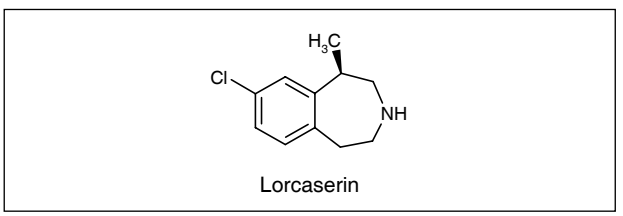
Cetilistat



Tesofensine



Otenabant HCl



Lorcaserin

glycogen stores, which leads to a rapid switch to fat utilization.

The first model discussed was the ventromedial hypothalamic (VMH)-lesioned rat. It was noted that these animals are obese, hyperphagic and hyperinsulinemic. The animals also display altered metabolism and activity. However, while hypothalamic lesions can cause obesity in humans, this is not common. This casts doubt on whether the control systems in this model are widely relevant to human obesity.

The leptin system has been shown to be important in the regulation of energy balance in humans (2). As a result, animal models have been designed around a leptin-deficient phenotype (3). *Ob/ob* and *db/db* mice were noted to exhibit human-like clinical presentations, with their obesity being largely hyperphagia-driven. However, the leptin profile of these animals was noted to be oppo-

site that of normal obese patients. Zucker diabetic fatty (ZDF) and corpulent (Cp) rats all have mutated leptin receptors. The ZDF rat phenotype is very similar to the *ob/ob* mouse. ZDF rats, like *db/db* mice, become diabetic. Cp rats, the numerous strains of which are developed from spontaneously hypertensive rats, have a more pronounced cardiovascular phenotype.

Diet-induced obesity (DIO) models were also discussed, with attention being brought to the many diets and many strains of animals used in these experiments. Palatability of the diet was shown to significantly affect the rate of weight gain. Duration of the diet brings about varying metabolic consequences, particularly with regard to insulin resistance. It was also shown that C57Bl6 mice are relatively resistant to DIO, but show high insulin and glucose intolerance. Conversely, AKR mice show more weight gain but better glucose homeostasis.

The speaker summarized that multiple rodent models are available, and researchers should choose appropriately. DIO models are perhaps closest to human obesity, while genetic models give greater severity in terms of metabolic syndrome. Both genetic and DIO models respond similarly to pharmacological treatments.

Stephen Bloom (Imperial College, U.K.) presented on the promise shown by gut hormones as the basis of a novel approach to obesity treatment. Gut hormones are released in response to a meal, acting on both central neural circuits and peripheral tissues. They affect diverse physiological functions, including appetite, gastrointestinal motility and acid secretion, nutrient absorption and cell proliferation. Receptors for gut hormones can be found on neuronal populations within the arcuate nucleus of the hypothalamus. Recent work has identified the gut hormone peptide YY (PYY), oxyntomodulin and pancreatic polypeptide (PP), which inhibit appetite, and ghrelin, which stimulates appetite.

PYY is a 36-amino-acid peptide, first isolated by Tatemoto's group in 1982 from pig gut extracts. It is produced by gut endocrine cells in both the small and large intestine and released into the circulation. Infusions in man at physiological concentrations have been shown to delay gastric emptying. Postprandial secretion of PYY increases with increasing caloric content of the meal. Circulating PYY levels are elevated 5-fold following major small intestine resection. Malabsorption, whether sprue, pancreatic failure- or drug-induced, leads to significant increases in PYY levels, as does acute gut infection. Administration of PYY reduces food intake in both lean and obese subjects, coupled with reduced hunger scores and reduced plasma ghrelin levels.

Oxyntomodulin is a 37-amino-acid gut hormone that is released into the plasma in relation to meal size. Levels are markedly elevated in bowel conditions such as pancreatic failure, tropical malabsorption and postsurgery short bowel syndrome, all of which are characterized by anorexia. Chronic (i.p.) oxyntomodulin administration reduced body weight gain in rats. Oxyntomodulin infusion led to reduced food intake and increased energy expenditure in humans, resulting in weight loss. Oxyntomodulin is susceptible to enzymatic degradation and renal clearance. The design of oxyntomodulin analogues has targeted amino acid substitutions, peptide chain extension and side-chain derivatization, with the objectives of increasing potency and duration of effect. The effects of oxyntomodulin have also been shown to be additive to the effects of the cannabinoid CB_1 antagonist rimonabant in reducing food intake in mice.

Infusion of human PP for 90 min was shown to reduce energy intake during a buffet meal 1 h later and over the following 24 h. PP administration reduced food intake in mice, although coadministration with PYY was less effective than when either compound was administered alone. Similarly, coadministration of PP and PYY in a clinical study looking at energy consumed during a free buffet meal was ineffective, while PP alone significantly reduced energy consumption.

Peptides were suggested to be better targeted drugs as they:

- Are composed of amino acids
- Mimic physiology
- Have limited CNS penetration
- Are given by injection

Sharon Cheetham (RenaSci, U.K.) described the discovery and development of one of the drugs that is now on the market to treat obesity. Sibutramine (or rather two of its metabolites) is an inhibitor of both NE and 5-HT uptake (Table I). It was originally developed as an antidepressant agent, but no effect was observed in a phase II trial of 1,000 patients. However, sibutramine was found to produce a dose-dependent decrease in body weight in the depressed patients. On this basis, sibutramine entered phase III clinical development as an antiobesity agent with weight loss as the efficacy endpoint demanded by the FDA Psychiatry Division. However, the FDA then created a Neuroendocrine and Metabolic Division, which indicated that weight loss was a "cosmetic endpoint" and approval would be based on reductions in cardiovascular risk factors.

Another challenge in the development of sibutramine as a treatment for obesity came in 1997 with the withdrawal from the market of both fenfluramine and dexfenfluramine. A combination of fenfluramine and phentermine ("Fen-phen") had been widely used off-label for the long-term management of obesity but was found to cause rare cardiac valvular disease in women. Also, the use of anorexic drugs (mainly derivatives of fenfluramine) was

Table I: Affinity of sibutramine and its metabolites for monoamine uptake sites in human brain.

	K_i (nM)	
	NE	5-HT
Sibutramine	5451	298
Metabolite 1	20	15
Metabolite 2	15	20

associated with an increased risk of primary pulmonary hypertension. As fenfluramine releases serotonin from nerve terminals, there were concerns that sibutramine would cause similar side effects, but no such evidence was obtained, which allowed the FDA to approve sibutramine (Meridia®; Abbott) for the treatment of obesity in 1997, although the product label contained the "baggage" of other drugs, and worse, the FDA/DEA placed it in Schedule IV. In Europe, having mandated 2-year efficacy data, the label allowed only 1-year treatment. The EMEA mandated a phase IV outcome trial, The Sibutramine Cardiovascular Outcome (SCOUT) trial, to determine whether long-term weight loss would improve morbidity and mortality in obese subjects at high cardiovascular risk – a patient population in which the drug is not recommended for use. The study is currently ongoing. Presently, both the FDA and the EMEA demand that any antiobesity drug should produce significant weight loss: 5% and 10%, respectively, for the FDA and EMEA. Another requirement is that any drug-induced weight loss be sustained and yield a significant reduction in risk factors for a number of obesity-related comorbidities.

Peter J. Richardson (Biovitrum, U.K.) described leptin, a 16-kDa protein hormone derived from fat cells that plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism, largely through its actions in the hypothalamus.

The effects of leptin were first observed in the U.S. in 1950 through the discovery of mutant mice that arose at random within a mouse colony that were massively obese and hyperphagic. Leptin itself was discovered in 1994, again in the U.S., through the study of such mice. The *Ob(Lep)* gene (Ob for obese, Lep for leptin) is located on chromosome 7 in humans. Leptin is produced by adipose tissue and interacts with six receptor subtypes (LepRa-f). LepRb is the only receptor isoform that contains active intracellular signaling domains and is located in a number of hypothalamic nuclei. Leptin signals to the brain that the body has had enough to eat (satiety) and a very small group of humans possess homozygous mutations for the leptin gene which leads to a constant desire for food, resulting in severe obesity. This condition can be successfully treated by the administration of recombinant human leptin.

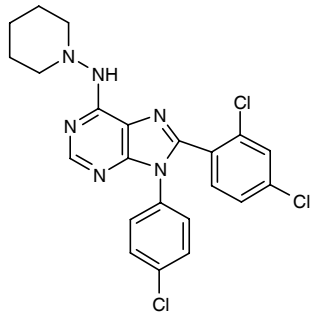
On this basis, Cambridge Biotechnology (now Biovitrum) initiated a research program to discover small-molecule leptin mimetics capable of entering the CNS. Leptin enters the brain by a saturable transport system, leading to treatment resistance, as elevated concentrations in the plasma of humans do not lead to high concentrations in the cerebrospinal fluid (CSF) (4). A small-molecule leptin mimetic would therefore be free of this constraint, as it should be capable of crossing the blood–brain barrier by passive diffusion.

After identification of the minimum active fragment of leptin, a peptide-mimetic approach was used to identify a series of stable small-molecule agonists. They were shown to bind to the leptin receptor and stimulate the phosphorylation of AKT in cells expressing the recombinant receptor. Optimization of potency and ADME properties was carried out using in vivo assays and the optimized leads were shown to mimic the effects of leptin on individual hypothalamic neurons (both hyperpolarizing and depolarizing), but to have no effect on neurons that do not respond to leptin. A key observation was that rats that were rendered obese by a high-fat diet were resistant to treatment with leptin, while the leptin-mimetic compounds caused a reduction in food intake and weight. It is highly likely that the antiobesity efficacy of the leptin mimetics is via leptin signaling, as no effect was seen in *db/db* mice, which have a defective leptin receptor.

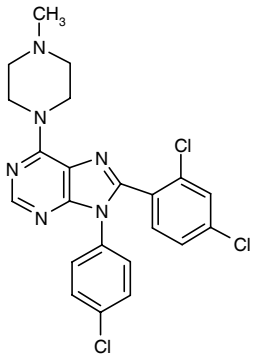
David Griffith (Pfizer, U.S.) presented the design and synthesis of the novel cannabinoid type 1 (CB_1) receptor antagonist otenabant. The endocannabinoid system has been shown to be dysregulated in patients with obesity and clinical data from multiple groups have shown CB_1 receptor antagonists to be effective in reducing body weight. The most advanced CB_1 antagonist is rimonabant (SR-141716A, Acomplia®) from sanofi-aventis, which was marketed in Europe from 2006 until its withdrawal in 2008. The approach taken at Pfizer was to investigate constrained analogues of rimonabant. The prototype for the series was a purine, compound **1**, which showed K_i values of 3.6 nM for rat CB_1 receptors and 7.4 nM for human CB_1 receptors (values for rimonabant were 0.7 and 1.3 nM, respectively).

Initial analogues in the series, with small lipophilic head groups, suffered from poor solubility and high clearance. A strategy was developed to address this through the introduction of polarity, although the structure–activity relationships (SAR) for the series presented few opportunities for this approach. Introduction of a piperazine in compound **2** provided a breakthrough, improving solubility while retaining a K_i of 5.2 nM at the human CB_1 receptor. However the piperazine **2** exhibited high clearance in rats and potent hERG activity (IC_{50} = 0.35 μM). These deficits were addressed through the introduction of a polar substituent adjacent to the basic nitrogen, while taking care not to push the polar surface area too high and impair permeability. This led to the discovery of otenabant.

Otenabant showed subnanomolar potency at human CB_1 receptors in binding (K_i = 0.7 nM) and functional assays (K_i = 0.1 nM), with low affinity (K_i = 7600 nM) for



Compound **1**



Compound **2**

human CB_2 receptors. In vitro the compound acted as an inverse agonist at the CB_1 receptor, as assessed in a [^{35}S]GTPγ binding assay. In vivo, otenabant potently reversed cannabinoid agonist-mediated responses, behaving as a neutral antagonist, with no effect on analgesia, hypothermia or catalepsy in the absence of agonist. Otenabant reduced food intake and increased energy expenditure and fat oxidation in rodents. Despite the impaired CNS penetration observed in rodents, pharmacokinetic/pharmacodynamic projections predicted human efficacy at doses below 100 mg. Otenabant is currently in phase III development for weight management.

Dominic Behan (Arena Pharmaceuticals, U.S.) described the pharmacological and clinical evaluation of lorcaserin, a novel and selective 5-HT_{2C} receptor agonist for the potential treatment of obesity. 5-HT_{2C} receptors are localized in the hypothalamus and there is evidence from experimental animals to suggest that agonists at this receptor hold promise for the treatment of obesity. Behan described the pharmacological and early clinical characteristics of lorcaserin, a selective, high-affinity 5-HT_{2C} full agonist (Table II). Behavioral observations in rats indicated that, unlike the 5-HT_{2A} agonist 2,5-dimethoxy-4-iodoamphetamine (DOI), lorcaserin did not induce behavioral changes indicative of functional 5-HT_{2A} receptor-agonist activity. In rats, lorcaserin acutely reduced food intake and chronic daily treatment over a 4-week period produced dose-dependent reductions in food intake and body weight gain in animals maintained on a high-fat diet.

To evaluate weight reduction and safety of lorcaserin in humans, 469 obese patients (men and women aged 18-65 years with BMI of 30-45 kg/m^2) were dosed during a 12-week period. Patients were randomized to placebo, lorcaserin 10 mg once daily, lorcaserin 15 mg once daily or lorcaserin 10 mg b.i.d. for 12 weeks and counseled to maintain their usual diet and activity. In patients completing the trial, lorcaserin was associated with progressive weight loss of 1.8, 2.6 and 3.6 kg, respectively, at 10 mg once daily, 15 mg once daily and 10 mg b.i.d. compared to 0.3 kg for placebo ($P < 0.001$ for each group). Similar results were seen by ITT-LOCF analysis. The proportion of patients achieving a reduction of at least 5% of initial body weight was 12.8%, 19.5%, 31.2% and 2.3%, respectively, in the lorcaserin 10 mg once daily, 15 mg once daily, 10 mg b.i.d. and placebo groups. The most frequent adverse events were transient and mild to moderate headache, nausea and dizziness, which tended to occur during the first few days of the trial. Echocardiograms showed no apparent drug-related effects on heart valves or pulmonary artery pressure. In conclusion, lorcaserin was well tolerated and effective for weight reduction in this 12-week study. It therefore has the potential to be an effective drug to regulate appetite and control body weight.

The metabolic abnormalities found in obesity and metabolic syndrome resemble those seen in Cushing's syndrome, an endocrine disorder caused by high levels of cortisol (a glucocorticoid) in the blood. However, there is no elevation in cortisol in the metabolic syndrome, which suggested that intratissue concentrations of glucocorticoids are critical to the regulation of adiposity and glycemic control.

11β-Hydroxysteroid dehydrogenase (11β-HSD) enzymes are responsible for the interconversion of active and inactive glucocorticoids (cortisol and cortisone, respectively, in humans; Fig. 1) and thus regulate the intratissue concentrations of active cortisol. Inhibition of the oxidoreductase activity of 11β-HSD1 would reduce intracellular cortisol concentrations, particularly in liver and adipose tissue, and result in decreased hepatic glucose output and a reduction in adipocyte differentiation. Validation of this hypothesis by preclinical and ultimately clinical evaluation of selective inhibitors of 11β-HSD1 has been the subject of intense efforts for a number of years, but these studies have been compromised by the species selectivity of many of the compounds.

Rachel Mayers (AstraZeneca, U.K.) described preclinical data using rodent-active inhibitors of 11β-HSD1 in a number of mouse models of the metabolic syndrome. 11β-HSD1 inhibition reduced adipose depot mass. However, the suitability of preclinical models may not have been optimal for predicting glycemic control in humans. Recently released phase IIa data from Incyte demonstrated improved hepatic insulin sensitivity in a euglycemic–hyperinsulinemic clamp study in patients with type 2 diabetes.

Table II: Affinity, potency and efficacy of lorcaserin at human 5-HT_2 receptors.

	5-HT_{2C}	5-HT_{2A}	5-HT_{2B}
Affinity (K_i, nM)	15	112	174
Potency (EC_{50}, nM)	9	168	943
Efficacy (% 5-HT)	100	75	100

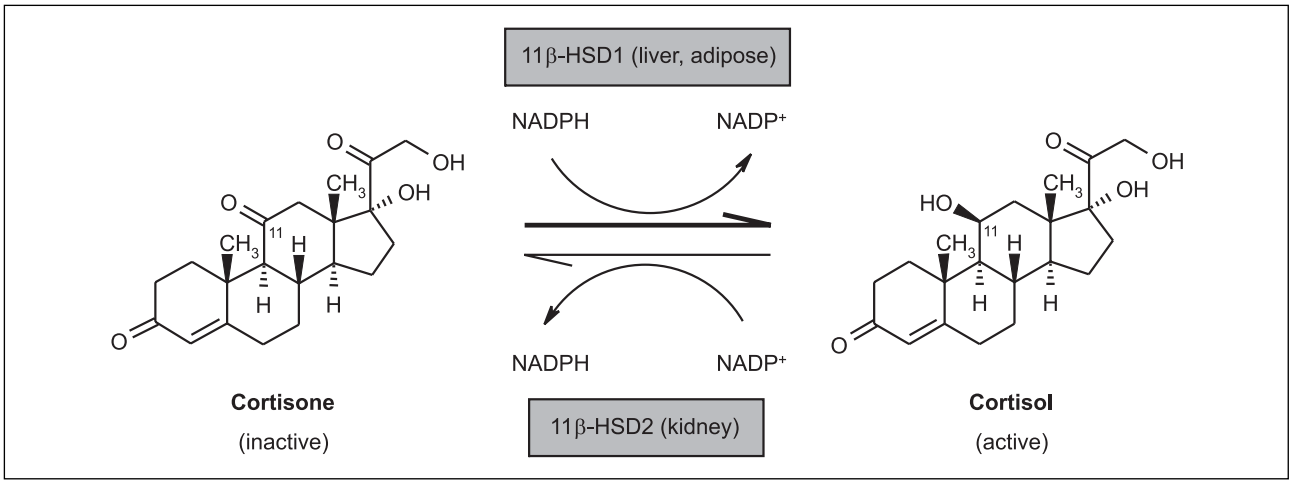


Fig. 1. Interconversion of cortisone and cortisol mediated by 11β-hydroxysteroid dehydrogenase (11β-HSD).

There is substantial evidence to indicate that endogenous hypothalamic serotonin plays a key role in within-meal satiation and postmeal satiety processes. The serotoninergic system has thus provided a viable target for weight control critical to the action of at least two effective antiobesity treatments, both producing clinically significant weight loss over a year or more. Numerous serotonin receptor subtypes have been identified; of these, serotonin 5-HT_{1B} and 5-HT_{2C} receptors have been specifically recognized as mediators of serotonin-induced satiety.

In summary, the meeting highlighted the importance of identifying new treatments for obesity, in terms of both the increasing prevalence and impact of the condition and the shortcomings of existing pharmacotherapy. A variety of novel therapeutic approaches were discussed, along with the state-of-the-art techniques to characterize and develop the compounds identified.

Disclosure

Phill Cowley (Schering-Plough, U.K.), Alan Palmer (MS Therapeutics, U.K.) and Robert Williams (Cancer Research, U.K.) are members of the Society for Medicines Research Committee (SMR; http://www.smr.org.uk/), which organizes conferences on behalf of the SMR. The SMR would like to thank Peakdale Molecular (http://www.peakdale.co.uk/) and Pharmidex (www.pharmidex.com) for their generous sponsorship of this meeting. Details of future SMR meetings can be obtained from the SMR Secretariat: 840 Melton Road, Thurmaston, Leicester, LE4 8BN, U.K. Tel: +44 (0)116 269 1048; Fax: +44 (0)116 264 0141; Email: secretariat@smr.org.uk.

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