MEETING REPORT

A report on the SMR Meeting on Anti-Obesity Drugs held on March 26, 1998, in London.

Update on Antiobesity Drugs

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Summary

The Society for Medicines Research organized a one-day meeting on antiobesity drugs on March 26, 1998, in London. Current environmental risks for obesity include an increase in the proportion of fat consumption—especially an increase in the fat-to-carbohydrate ratio—and an increase in a sedentary life-style without an appropriate lowering in food intake. Energy balance plays a pivotal role of in the control of body stores. Knowing the mechanisms of the control of energy intake and energy expenditure provides explanations for the incidence of obesity and also possible sites for drug intervention. The genetic basis for obesity is complex, with the probability of a number of interacting genes being involved (polygenic inheritance). Each of the main components of the energy balance relationship has a distinct genetic basis. The *ob* gene was first identified in 1994 by Friedman, and its product is leptin, which may well be a potential target for obesity treatment. Speakers at the meeting highlighted various targets that hold promise in developing pharmacological treatments for obesity: increasing the activity of satiety factors (CCK-8, GPL-1, ACTH, αMSH and 5-HT acting on 5-HT_{2C} receptors); inhibiting orexigenic agents (NPY, MCH, galanin); targeting thermogenesis (β_3-adrenergic agonists and uncoupling proteins); targeting fat absorption; and targeting neuropeptides. Some of the compounds developed to act on these sites are now becoming available.

The Society for Medicines Research organized a one-day meeting on antiobesity drugs on March 26, 1998, in London. The introductory remarks of Dr. N. Finer (Luton & Dunstable Hospital) and Prof. P. Trayhurn (Rowett Research Institute) set the scene for the day. The definition of disease is a disturbance and derangement of physiological functions. Based on this, obesity is a disease, and in addition it is a risk for other diseases. It causes psychological distress and it impairs the quality of life. In the Western world, obesity is a major disorder with more than 50% of the population overweight with a body mass index (BMI) greater than 25 kg/m^2; in the U.K., 16% of men and 18% of women are clinically obese (BMI > 30 kg/m^2). The incidence of this disease has doubled since the 1980s and is still rising, with an associated increase in mortality and co-morbid diseases such as diabetes, hypertension and coronary heart disease. A genetic predisposition to obesity accounts for 20–40% of cases, but environmental factors exert the most important contribution and are the cause of the increase seen in the last 20 years.

Dr. Finer and Prof. J. Blundell (University of Leeds) identified the current environmental risks, the main ones being an increase in the proportion of fat consumption and especially an increase in the fat-to-carbohydrate ratio. Thus, a desirable diet consists of 50% carbohydrate, 20% protein and 30% fat, while the typical U.K. diet is 40% carbohydrate, 20% protein and 40% fat (48% in school and canteen meals). This leads to greater weight gain than just eating more bulk, as fat has a weaker effect on the satiety center and on heat production (diet-induced thermogenesis), and it possesses a higher energy density compared to carbohydrates, thereby leading to passive overconsumption. Another environmental risk is an increase in a sedentary life-style without an appropriate lowering in food intake. This is correlated with socio-economic class, the poorest being the most inactive.

Understanding the control of body weight

Energy balance regulation

In the first talk of the symposium, Prof. M. Stock (St. George's Hospital Medical School) described the pivotal role of energy balance in the control of body stores. The relationship can be expressed as: Energy Intake = Energy Expenditure ± Body Energy Stores with a homeostatic interaction between intake and expenditure. Taking each component in turn, energy intake is dependent on appetite, which in turn is controlled mainly by glucostatic and lipostatic feedback systems. On the other side of the equation, energy expenditure is dependent on heat production (diet-induced thermogenesis; DIT), metabolism (basal metabolic rate; BMR) and physical exercise. In the normal subject, DIT accounts for 10–12% and BMR for 65% of energy expenditure, with physical activity being a variable component. The rest of the energy intake is converted into body stores, which will increase if any of the forms of expenditure are reduced. In those susceptible to obesity, DIT—and more rarely BMR—are lower than normal (DIT can be 0–5% vs. 10–15% in those more resistant to obesity). The problem with reducing intake, namely, dieting, is that energy intake and expenditure are positively related, so if there is a reduction in intake there is a compensatory reduction in DIT and BMR and, therefore, less weight loss.

Knowing the mechanisms of the control of appetite (energy intake) and energy expenditure provides explanations for the incidence of obesity and also possible sites for drug intervention. Professors Blundell and G. Williams (University of Liverpool) described the control of appetite (see later), while Prof. Stock focused on the control of diet-induced thermogenesis.

Eating results in sympathetic nervous system activation of thermogenesis in brown adipose tissue (BAT) via an atypical β_3-adrenoceptor (β_3AR) and a mitochondrial uncoupling protein (UCP-1) that is unique to BAT. This activation leads to uncoupling of oxidative phosphorylation without ATP production and so induces oxidation of fatty acids and/or energy dissipation as heat. β_3ARs are also present in white adipose tissue (WAT), and the newly discovered UCP-2 is present in BAT and many other tissues, while UCP-3 is present in skeletal muscle (and BAT, at least in rodents). It follows then, that stimulation of the sympathetic system will increase metabolic rate, while inhibition will reduce the oxidation of fat and thermogenic responses to feeding. On dieting, sympathetic activity is reduced in proportion to weight loss and so there is a decrease in thermogenesis. A useful adjunct to dieting, therefore, is a sympathomimetic such as a β_3AR agonist, which would increase or maintain heat production in spite of the reduced food intake. As mentioned in the next section, mutations of the human gene for β_3AR and UCP-1 may be linked to a predisposition to obesity.

Genetic obesities

Prof. Trayhurn described the genetic basis for obesity, which is complex, with the probability of a number of interacting genes being involved (polygenic inheritance). Each of the main components of the energy balance relationship—energy intake, BMR, the thermic effect of food and physical activity—has a distinct genetic basis. There is also a genetic component to body fat distribution. Information on a genetic basis for obesity comes from studies on populations, families and twins and from adoption studies.

There are several inherited disorders in humans associated with obesity, for example, Prader-Willi's (1 in 20,000 children), Cohen's, Carpenter's and Bardt-Beadle's syndromes. In other species, there are clear examples of a genetic basis to body fat content, with major differences in the tendency to fatness between strains; for example, Pietrain and Landrace pigs are lean, while the Chinese Meishan pig has a high body fat. Candidate gene approaches have been employed in attempts to determine whether particular genes may be linked to obesity. Specific polymorphisms in the uncoupling protein-1 gene (expressed in BAT) and the β_3AR gene have both been associated with a higher body fat, and there appears to be an additive effect of the two polymorphisms.

The clearest link between genes and obesity is most obvious in laboratory rodents, where there are strains in which frank obesity results from mutation of a single recessively inherited gene. The best known is the *ob* gene, which encodes the adipocyte-derived hormone leptin. Mice carrying this gene have excess WAT, are diabetic and are sterile. Other such genes that have been cloned in the last four years include *db*, *fa*, *fat* and *tub*. The *db* and *fa* mutations (homologues) relate to the gene encoding the receptor for leptin, and the *fat* mutation to the gene encoding carboxypeptidase E. Analysis of the rodent obese mutants has led to the discovery of a "new" regulatory system based on the lipostatic model of the control of energy balance.

Leptin: Activity, target and control

The *ob* gene was first identified in 1994 by Friedman, and its product is leptin (Greek for "thin" or "small"). It is produced by WAT and is thought to pass into the circulation and then be transported to the brain. Leptin can pass into the CNS through a modified area of the blood–brain barrier near the arcuate nucleus or via the choroid plexus, where short-form leptin receptors are sited which transfer leptin to the hypothalamus. Once within the CNS, leptin acts on specific long-form receptors (Rb) to stimulate satiety. Thus, leptin is a mediator of a negative feedback control on WAT. However, the biology of leptin is much more complex than this, as it not only controls food intake, but also activates energy expenditure—or at least prevents adaptive falls. Leptin is also involved in reproduction, hemopoiesis and glucose metabolism.

Experiments in rodents show that leptin reduces food intake and body

weight but only over the period of treatment. It is much more effective in the *obob* mouse (which is completely deficient in leptin) than in the lean, and can reduce food intake in the former by 50–80%.

Leptin is now known to be synthesized in WAT, BAT and the placenta, and other sites may be identified in the future. Its production in WAT is reduced by fasting, cold and exercise, as well as sympathetic activity acting on β_3ARs. Testosterone, thyroid hormone and thiazolidinediones are also inhibitory, while leptin production is enhanced by feeding, fever, insulin, glucocorticoids and cytokines.

There are six splice variants of the leptin receptor, designated Ra, b, c, d, e and f. Rb is a long form and appears to mediate the main effects of leptin; the rest are short forms and some may act as transporters for leptin. The ob-Rb receptor is found mainly in the brain, which seems to be the major target site, but there are also receptors in the testes, adipose tissue, heart, liver, placenta and spleen, which suggests that many peripheral actions have yet to be revealed. Focusing on brain sites, the hypothalamus is the most important, especially the paraventricular, ventromedial and arcuate nuclei (all involved in control of energy balance), but other sites for the receptors are the choroid plexus, brain stem, cortex and leptomeninges. The presence of leptin receptors on NPY, POMC and GLP-1 neurons indicates that interactions occur between leptin and other CNS peptidergic neurotransmitter systems.

The leptin regulatory system is present in humans, and leptin plasma levels fluctuate with fasting and changes in insulin. Obese subjects have very elevated circulating levels of leptin, and based on these, it is hypothesized that human obesity is linked to leptin resistance; however, there is no direct evidence for this and the obese may just be behaviorally indifferent to the high levels resulting from their excessive fat deposition. Recently, Montague et al. (*Nature* 1997; 387: 903–7) observed a mutation in the *ob* gene associated with obesity in two children, and leptin receptor polymorphisms also have been linked to obesity in three sisters (Clement et al., *Nature* 1998; 392: 398–401).

Thus, leptin may well be a potential target for obesity treatment where perhaps beneficial effects may be obtained by increasing leptin production, decreasing its removal, increasing the ratio of free to bound leptin, increasing its passage through the blood–brain barrier, synthesizing leptin mimetics and/or sensitizers or even by acting downstream on intracellular signaling interfering with leptin's interactions with other neurotransmitter systems.

Psychobiology of appetite and neuropeptides as targets for anti-obesity drugs

Returning to the relationship of energy intake and expenditure explained in the first talk by Prof. Stock, Professors Blundell and Williams described the control of food intake, that is, the mechanisms that create a feeling of hunger or satiety. The system can be shown depicted in Figure 1.

As far as eating behavior is concerned, the important point is that food intake is a balance of 1) drive for food, which is controlled by tonic signals to the brain associated with metabolism and energy expenditure; and 2) satiety, which is controlled by food ingestion and is an intermittent control. The system depicted in Figure 1 is normally tightly regulated and maintains a stable body weight for long periods. Obesity is the result of a defect in the system, which anyway tends to be asymmetric and permits overconsumption rather than underconsumption. The fact that obesity is increasingly prevalent indicates that the regulatory system is not working well in our modern society, and drugs that can strengthen the inhibitory signals may help to overcome the defects.

Prof. Williams listed a number of CNS and peripheral signals that control appetite, including hyperphagic neurotransmitters: neuropeptide Y (NPY), galanin, opioids, melanin-concentrating hormone (MCH); hypophagic neurotransmitters: neurotensin, bombesin, glucagon-like peptide-1 (GLP-1), α-melanocyte–stimulating hormone (αMSH), corticotropin-releasing hormone (CRH), cholecystokinin (CCK), noradrenaline and 5-HT. Then Professors Blundell, R. Ganellin (University College, London) and Williams highlighted various specific agents that hold the most promise in developing pharmacological treatments.

Cholecystokinin-8. Professors Blundell and Ganellin focused on cholecystokinin (CCK), which is secreted from the duodenum and, acting on CCK_A receptors in the stomach wall, stimulates vagal afferents to the paraventricular nucleus (PVN) to suppress food consumption. It also aids digestion by inducing gallbladder emptying and stimulating the pancreas. The sulfated form of CCK is 100% more potent, but its actions are unfortunately short lived, so that if administered before a meal it will suppress hunger, but soon after hunger increases rapidly since less food has been consumed. A search for longer-lasting analogues is ongoing, as described by Prof. Ganellin, who also provided data from his laboratory on a newly synthesized inhibitor of CCK degradation (see later).

Neuropeptide Y. This is the most abundant in the brain, with its highest levels in the hypothalamus, especially the feeding centers. Its cell bodies are sited in the arcuate nucleus (ARC) and project to the PVN and dorsomedial nucleus (DMN), and there are binding sites (probably the Y_5 receptor) in the lateral hypothalamus. Acting on Y_5 receptors, NPY increases food intake, reduces thermogenesis in brown fat, increases insulin levels (by stimulating vagal outflow to the pancreas) and reduces muscle sensitivity to insulin. It increases the triglyceride content in white fat and after five days' treatment (intracerebrally) doubles fat stores in

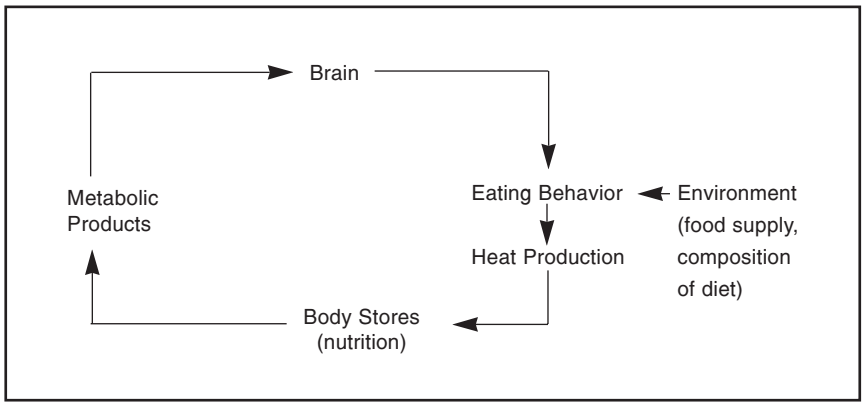

Fig. 1. Schematic depiction of the control of food intake.

both lean and *obob* mice. NPY expression is increased in the ARC, PVN and DMH in the *obob* mouse and Zucker rat and helps account for their increased eating and decreased thermogenesis. The NPY neurons in the ARC possess glucocorticoid, insulin and leptin receptors, and it seems likely that leptin has an inhibitory effect via the Rb receptors on the NPY neurons because it reduces feeding, increases thermogenesis and, at the same time, reduces NPY mRNA, NPY protein and NPY release.

α-Melanocyte–stimulating hormone. Pro-opiomelanocortin (POMC) neurons exist in the ARC and nucleus stria terminalis, and release αMSH, which acts on MC_4 receptors to reduce feeding. The physiological significance of this is indicated by the up-regulation of MC_4 receptors in food deprivation, presumably resulting from inhibition of αMSH release. The Agouti mouse model overexpresses an endogenous MC_4 inhibitor (agouti protein) and this model is, as expected, obese. MTII is an αMSH analogue that acts like αMSH and prevents overeating; it also has the other actions of αMSH and tans skin, darkens hair and stimulates erection.

When targeting neuropeptides as forms of treatment, Prof. Williams suggested increasing the activity of satiety factors (CCK-8, GPL-1, ACTH, αMSH and 5-HT acting on $5\text{-}HT_{2C}$ receptors) and inhibition of orexigenic agents (NPY, MCH, galanin) by enhancing the availability of the former (stimulating release, inhibiting re-uptake and agonist analogues) and reducing the availability of the latter (inhibiting release, increasing re-uptake and postsynaptic receptor blockers).

Appetite and monoamines

It has long been known that the monoamines, that is, noradrenaline and serotonin (5-HT), acting within the CNS influence appetite, and drugs that enhance their activity have been or could be used clinically. Prof. Blundell and Dr. P. Kopelman (St. Bartholomews and Royal London School of Medicine and Dentistry) listed some of the agents which included 5-HT precursors (tryptophan and 5-hydroxytryptophan), selective serotonin re-uptake inhibitors (e.g., fluoxetine), combined serotonergic and noradrenergic re-uptake inhibitors (e.g., **sibutramine**), selective 5-HT–releasing agents (e.g., **fenfluramine** and **dexfenfluramine**) and nonselective releasing agents (e.g., **phentermine**, which acts to enhance noradrenaline release more than 5-HT release). Dr. Kopelman described the clinical uses of some of these drugs (see later).

Clinical management of obesity

Consequences and management of obesity

Dr. Finer described the prevalence, risk and management of obesity. Obesity is associated with increased mortality and morbidity, and analyzing this further, it is the pattern of disposition of the fat that is actually associated with risk. An "apple shape" (i.e., central visceral obesity) is more dangerous than a "pear shape" (i.e., gynoid, with subcutaneous fat on the hips and thighs), and a high waist:hip ratio is associated with high mortality.

Complications associated with obesity include diabetes, where there is a 77 times greater risk of non–insulin-dependent diabetes mellitus (NIDDM) if the BMI is greater than 25 kg/m^2; in women, 90% of NIDDM is due to obesity. Other associations include hypertension, respiratory disorders, cancer—particularly of the colon—, fatty liver and gallstones. Losing weight reduces all these co-morbidities, so rather than treat each disease it would be more effective to treat the obesity itself.

Treatments can be divided into three types:

- Surgical, such as vertical banded gastroplasty, which reduces the size of the stomach and is highly effective in reducing food intake and the associated diseases of obesity (e.g., NIDDM, [14-fold reduction], hypertension [three- to fourfold reduction]); it also relieves depression and anxiety.
- Dietary, with or without group behavior programs with psychologists and nutritionists. This focuses on reducing diet, altering feeding patterns and increasing exercise. There is a high failure rate in terms of maintenance using this method.
- Drug treatments in association with diet in order to facilitate and then help maintain weight loss. The potential sites of the drugs are the controls of energy intake, energy expenditure or both.

In general, all treatments that reduce weight have benefits in reducing co-morbidity and enhancing the quality of life.

Use of monoamine appetite suppressants

Dr. Kopelman listed the main drugs in clinical use that enhance monoamine activity, most of which have been itemized above, and went on to describe their effects in the clinic. The drugs that are or have been in use recently include **fenfluramine**, **dexfenfluramine**, **phentermine** and **sibutramine** (Fig. 2); all can induce 10–12% loss in body weight in three months and often a 5–10% loss will be maintained for 12 months. However, inexplicably, this only occurs in 30% of patients, the rest being nonresponders. These can be identified as early as 1–3 months after treatment starts, and it is important to recognize the nonresponders, since obviously the risks will then outweigh the nonexistent benefits.

The use of **fenfluramine** (fen) in Europe over the last 30 years and of **dexflenfluramine** (dex) over eight years has shown that potential CNS effects of these drugs are not a risk. However, more recently (1996), concern was expressed in the United States over the association of **fenfluramine** and **phentermine** (fen–phen) therapy, with a 30-fold increase in primary pulmonary hypertension. The odds ratios were 1.8 and 23.1 with treatment of less than three months and more than three months, respectively, with the normal annual incidence in the general population being 1 in 500,000. This warning was followed by a study in the United States on 24 women (average age 44 years) given fenfluramine for 12 months and undergoing echocardiography which revealed unusual valvular morphology and regurgitation in all cases with both the right and left valves involved. There were abnormal plaques of gelatinous material present which encased the leaflet and chordal structures and gave a "glistening" appearance to the valves. Eight of the 24 subjects had pulmonary hypertension. A separate type of valvular heart disease has been associated with dexflenfluramine, with enlarged veins due to arteriole thrombotic occlusion.

In 1997 the U.S. FDA reported cases of cardiac valve abnormalities associated with these appetite-suppressant drugs: 79% associated with fen–phen, 14% with dex, 7% with fen and 5% with dex–phen, phen alone and dex–phen–fen. Of these, 27 subjects underwent valve replacement and there were three postoperative deaths. In Europe between 1992 and 1997, there were 43 cases of valvular abnormalities associated with appetite suppressants. In view of these findings, the fenfluramines were withdrawn from the international market by the manufacturer in September 1997.

Is this deleterious effect due to increased monoamine activity or to weight loss? There have been no published cases associating pulmonary hypertension with other selective serotonin re-uptake inhibitors used in the treatment of depression, so perhaps 5-HT is not involved. On the other hand, **fenfluramine**, **dexfenfluramine** and **aminorex** (another agent that releases monoamines) can inhibit potassium ion passage in pulmonary vascular smooth muscle, leading to vasoconstriction, which in turn may lead to hypoxia and the hypoventilation syndrome. Another cause may be the weight loss itself, which tends to reduce left ventricular mass and may lead to pulmonary hypertension. Further studies are needed, but in the meantime while the symptoms seem associated with the monoamine releasors rather than the uptake inhibitors, the registration of any monoamine-releasing agent could only be justified for seriously obese patients with related diseases. It should be noted that since the withdrawal of the fenfluramines, the FDA has approved the use of **sibutramine**, which is a monoamine re-uptake inhibitor and not a releasing agent.

The search for new antiobesity drugs

Targeting thermogenesis: β_3-Adrenergic agonists and uncoupling proteins

Dr. J. Arch (SmithKline Beecham Pharmaceuticals) and Dr. A. Shuker (Eli Lilly and Co.) provided a summary of our current knowledge of the β_3-adrenergic receptor (β_3AR) and β_3-agonist activity. The human β_3AR was cloned in 1989 and has a 78% homology with the rat receptor. It is a 7-transmembrane G-protein–coupled receptor and has 47% homology with the β_1AR and the β_2AR. Stimulation of β_3AR activity in BAT increases thermogenesis and oxidizes and mobilizes fat. In WAT, β_3 activity hydrolyzes fatty esters to release free fatty acids. β_3AR activation has no effect on the heart (which is stimulated by β_1ARs), nor does it cause tremor, hypokalemia or bronchodilation (all due to β_2AR activity). It seems, therefore, that a selective β_3-agonist would be of great therapeutic value, and if combined with mild β_1- and β_2-antagonistic activity, it would be even more beneficial, especially in the obese patient with a stressed cardiovascular system.

Phenylethanolomines (e.g., **BRL-37344** and **CL-316243**; Fig. 2), aryloxypropanolamines (e.g., **CGP-12177**; Fig. 2) and **LY-104119** are all agonists with more affinity for the β_3AR than the β_1AR or the β_2AR, and on the rat receptor are very effective lipolytic agents which *in vivo* cause body weight and fat loss. However in humans, they perform poorly, often with side effects on the cardiovascular system and causing tremors, probably due to actions on the β_1AR and the β_2AR. Their ineffectiveness may be due to 1) differences in the human and rodent β_3AR; 2) differences in metabolism and pharmacokinetics in the rodent and humans; 3) because the human has fewer β_3ARs; or 4) because these receptors are less well coupled to thermogenesis. Obesity and diabetes are weakly associated with the $Trp^{64} \rightarrow Arg$ mutation of the β_3AR, which exerts a reduced intracellular transduction effect via cAMP. The lower levels of BAT in humans are unlikely to be a cause of the ineffectiveness, since even in the rat, BAT is not the only source of β_3AR-induced thermogenesis, and recently both β_3ARs and UCP-2 and UCP-3 have been identified in human skeletal muscle.

Recently, scientists at SmithKline Beecham Pharmaceuticals have

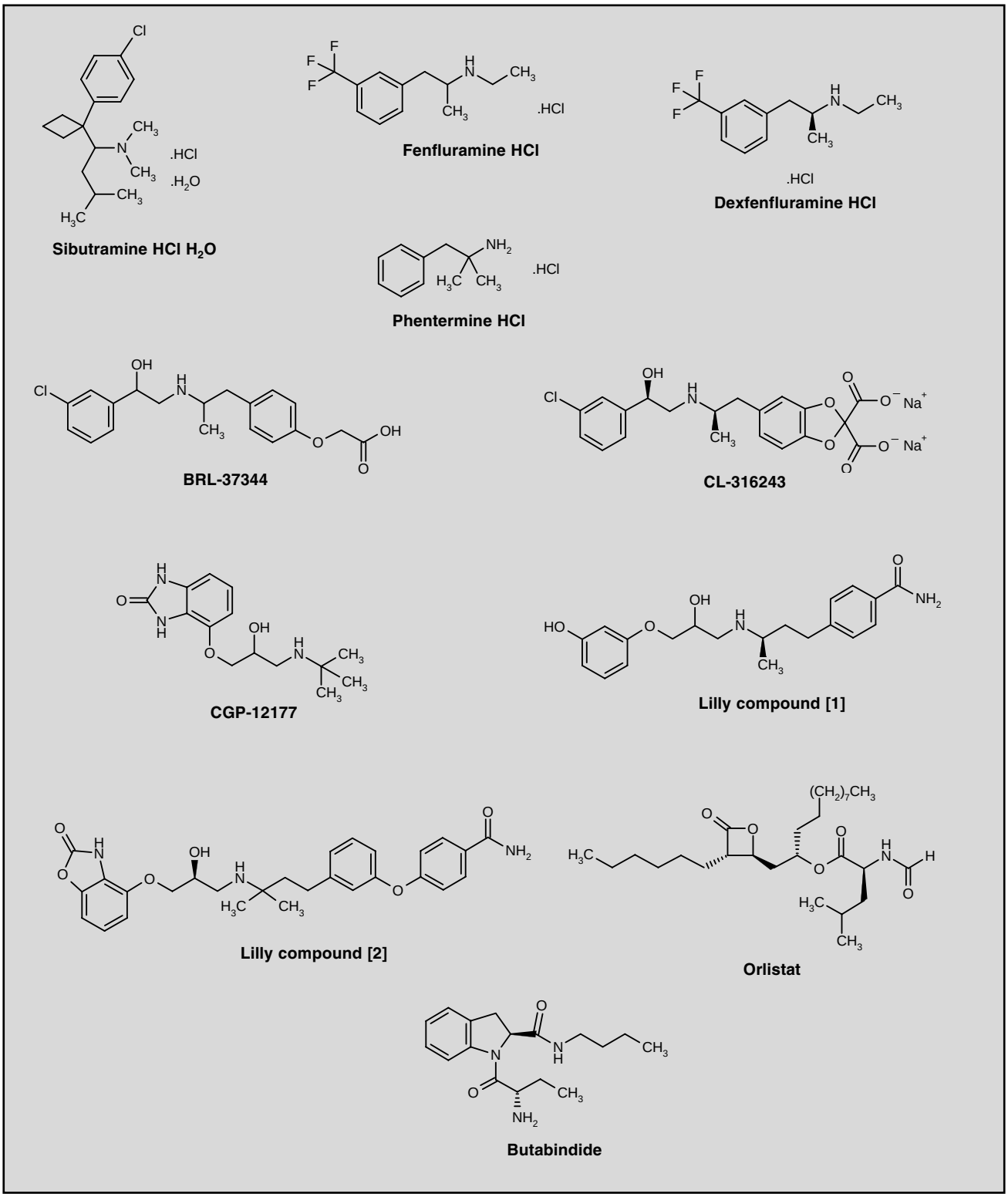

Fig. 2. Structures of compounds discussed at the meeting.

screened compounds using cloned β_3-receptors on WAT and noting stimulation of lipolysis. They have identified three compounds and compared them with the partial β_3AR agonist **CGP-12177** (Novartis AG), which has lipolytic activity on human WAT. **SB-220646** is a phenylethanolamine whose lipolytic effect can be blocked readily by propranolol, indicating that it is acting via β_1AR and β_2AR in WAT. It also has a full agonist effect on

human atrial tissue. **SB-226552** is a nonoaryloxypropanolamine and is a selective β_3AR agonist with no effect on the heart, but is tenfold less potent than CGP-12177. **SB-236923** is also an aryloxypropanolamine and a selective β_3AR agonist with potency similar to that of CGP-12177, but with some effects on the heart that can be blocked by propranolol (i.e., has some β_1AR activities).

Mitochondrial uncoupling proteins provide the link between the β_3AR and thermogenesis by allowing fatty acids released by lipolysis to be oxidized without forming ATP. UCP-1 is found in BAT, UCP-2 is widely distributed and UCP-3 is found in skeletal muscle, and in rodents in BAT. Other, as yet undiscovered, UCPs may exist. Agents that activate them or increase their expression offer a new therapeutic approach.

Dr. Shuker described another intensive screening strategy at Eli Lilly & Co. that also involved the human cloned β_3AR as the primary screen. They started with 500 compounds containing an ethanolamine moiety, from which 92 compounds with a reasonable activity were selected; further selection led through to one compound (**[1]**; Fig. 2) that had an EC_{50} of 30 nM but was compromised by oxidative liabilities and susceptibility to rapid glucuronidation of the phenolic OH group. Dr. Shuker described a combinatorial synthetic approach which allowed rapid and simultaneous analysis of the structure–activity relationships of the left-hand, middle and right-hand segments of the molecule. The synthetic methodology used a reductive amination reaction, with ion exchange purification to rapidly produce arrays of ethanolamines from the reaction of primary amines and ketones.

This led to compound **[2]** (Fig. 2), which had an EC_{50} of 30 nM against human β_3 receptors and evinced lipolytic effects in the Avy/a viable yellow obese mouse model. The compound was also evaluated for its effect on glycerol production on adipose tissue from obese patients, where it was found to produce effects at concentrations below 1 nM. However, the bioavailability of **[2]** was low, at no more than 18% in any animal species, and together with a high calculated lipophilicity of 4.2, this compound is not the most optimal available from the Lilly project. The validity of the β_3AR agonist approach to obesity still needs clinical validation, which is expected to be publicly available in the next 12–18 months.

Targeting fat absorption: Orlistat

Dr. J. Dallas (Roche Products Ltd.) summarized the clinical uses of **orlistat** (Fig. 2), which has just been given a positive opinion by the CPMP (March 1998). Orlistat inhibits pancreatic lipase, which normally converts triglycerides to free fatty acids and glycerol, which can then be absorbed. Orlistat only has a partial effect, inhibiting 30% of the lipase activity, allowing 70% of the fat intake to be absorbed while the rest passes through the lumen and out in the feces. The drug itself is only minimally absorbed and is also excreted in the feces. The recommended dose is 120 mg t.i.d., and higher doses have no extra effect. It is aimed for use in combination with other weight control methods (diet, exercise, etc.) and to produce a healthier lower body weight rather than an ideal one.

There have been seven clinical, two-year, double-blind trials which showed that **orlistat** in conjunction with a hypocaloric diet improved the maintenance of weight loss after one year by 10% in 30–40% of the subjects, which was double that of the controls on the diet alone. There was also a greater weight loss in 35% of subjects. In the second year there was a small rebound effect with an overall reduction of 8% at the end of trial, but this was partly due to a change back to a normal diet.

Other beneficial effects of **orlistat** are a reduction in blood pressure in subjects with a diastolic pressure greater than 90 mmHg and reduced LDL cholesterol, which continued downward with length of treatment, and in those with diabetes (insulin-dependent or not), orlistat improves glucose tolerance and allows a reduction in dose of insulin or sulfonylurea.

The main adverse effect of **orlistat** is the high fat content in the stools, causing oily spotting in 27% of patients and fecal urgency or even incontinence. This occurred in the first 2–3 weeks of treatment and can be controlled by reducing fat intake, and by the second year only 4% complained. This is mainly due to a tolerance mechanism in the distal bowel which allows for increased incorporation of oil into the feces. The potential problem of reduced levels of fat-soluble vitamins was carefully investigated; vitamins A, E and K were not affected and the slight reduction in vitamin D did not alter serum calcium ion levels, parathyroid hormone or bone density.

The FDA is still reviewing the use of **orlistat**, as there is concern over an increased incidence of breast cancer in orlistat-treated versus the nontreated population, but as stated above, the CPMP has given it a positive opinion.

Targeting neuropeptides: Design of butabindide, the first inhibitor of the CCK-8–inactivating peptidase

Prof. Ganellin summarized the actions of CCK (see above) and emphasized its short-lived half-life. The first approach was to design some long-acting CCK agonist analogues, and Glaxo Wellcome produced a series of 1,5-benzodiazapine structures (e.g., **GW7178**, which was orally active with a pIC_{50} of 7.1 on gallbladder emptying), but as all members of the series were peptides, they had poor bioavailability. Another approach was to extend the lifespan of CCK-8 itself and to this end, Prof. Ganellin's team focused on the degrading enzyme which breaks CCK-8 into smaller fragments that can be measured by HPLC methods (e.g., AspTyr(SO_3H)Met–GlyTrypMet–AspPhe-NH_2).

The search for enzyme antagonists used modified substrates incorporating

a fluorescent coumarin fragment and radioimmunoassays measuring CCK-8 itself and its degraded fragment Gly-Tryp-Met-OH. These techniques picked up the inhibitory effects of a range of serine protease inhibitors, but their nonspecificity was of concern. Chemically, the team had avoided serine-reactive groups, and has sought compounds likely to interact in a noncovalent fashion. They had to contend with an enzyme that was poorly characterized and was not yet available in a fully purified state, let alone having an X-ray crystal structure, which is the basis for modern structure-based drug design. Initially, they screened a di- and tripepide array, with compounds including nonnatural amino acids and a terminal amide replacement for the acid moiety found in CCK itself. The presence of a proline group in the center of the compounds conferred high activity and in addition offered rigidity and stability to endogenous peptidases. In a further round of modifications, the group reduced the number of amide linkages and produced **UCL-1397** (**butabindide**; Fig. 2).

This compound has an IC_{50} in the *in vitro* assay of 7 nM, but more than 1 μM against other proteases. *In vivo*, **butabindide** has an effect on gastric emptying at a dose of 10 mg/kg i.v. and at a similar dose reduces food intake in starved rats. This effect is blocked by devazepide, a CCK_A antagonist, but not by a CCK_B antagonist. Later work showed that the enzyme was identical to tripeptidyl peptidase II (TPPII; EC3.4.14.10), a protease whose existence, but not function, was previously known. It seems that TPPII may be the physiological CCK peptidase, as the highest hydrolysis rate was seen with this peptide, although it also acted, albeit at a lower rate, on neurokinin A, somatostatin and vasopressin.

Conclusion

The SMR symposium gave a detailed overview of our knowledge of the control of body weight, summarizing the control of energy intake (appetite, digestion and absorption) and energy expenditure (thermogenesis, basal metabolism and physical activity). These help to define sites for targeting and intervention in order to reduce intake and enhance expenditure. Some of the compounds developed to act on these sites are now becoming available. Two examples of those mentioned in the meeting are sibutramine and orlistat.

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PHASE I TOXICITY AND EFFICACY RESULTS FOR CT-2584 PRESENTED AT ASCO MEETING

The results from a U.S. phase I clinical trial of **CT-2584**, Cell Therapeutics, Inc.'s small-molecule anticancer/antiangiogenic agent, conducted at the Memorial Sloan-Kettering Cancer Center were presented May 18, 1998, at the 34th Annual Meeting of the American Society of Clinical Oncology in Los Angeles.

This study is designed to establish the maximum tolerated dose, pharmacokinetic profile and antitumor activity of CT-2584 in patients with advanced carcinoma. Patients are administered CT-2584 by six-hour i.v. infusion for three days followed by 18 days of no therapy; if no dose-limiting toxicity is observed during the first cycle, a second cycle is administered. Patients with stable disease or a reduction in tumor size after two cycles are eligible to receive a total of up to six cycles of therapy.

In this study, all 23 patients enrolled are evaluable for toxicity and 18 for tumor response. No dose-limiting side effects have been observed. Thirteen patients remain alive after a median of eight months, five of whom had disease stabilization.

Combined with the results from a similar study in progress in the U.K., over 50 patients have been treated with CT-2584 and 35 are evaluable for response. Ten of the 35 patients had disease stabilization and seven of these remain alive after a median of ten months following treatment. Overall, 21 of all 35 evaluable patients from both studies remain alive after a median of ten months after starting CT-2584 treatment.

CT-2584 has a unique mechanism of action which involves an effects on tumor cell phospholipids such as phosphatidic acid, and it also inhibits angiogenesis. Evidence suggests that the compound may be particularly effective in patients with advanced prostate cancer and sarcomas due to its combination of direct cytotoxic and potent antiangiogenic effects.

Cell Therapeutics plans to begin phase II trials this year in both advanced prostate cancer and sarcomas.