

Anti-obesity Drugs: From Animal Models to Clinical Efficacy

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INTRODUCTION	272
CLINICAL ASPECTS OF OBESITY AND CARDIOMETABOLIC DISEASE	273
Background – Do We Need Drugs for Obesity?	273
Current Drugs for Obesity and Their Limitations	274
Other Drugs – Withdrawn or No Longer Recommended for Routine Clinical Use	275
The Need for New Drugs	275
BIOLOGY AND GENETICS OF ENERGY REGULATION AND IMPLICATIONS FOR OBESITY	276
Short-Term (Episodic) Signals	276
Meal Onset	276
Meal Termination	277
Thermogenesis	278
Long-Term (Tonic) Signals	278
CNS Integrating Pathways	279
BIOMARKERS OF ENERGY REGULATION AND OBESITY	280
Anthropometric Measures	280
Measures of Adiposity	281
Measures of Energy Expenditure	281
Risk Factors	282
Insulin Resistance and Systemic Inflammation	282
THE PSYCHOBIOLOGY OF APPETITE EXPRESSION	283
Episodic Signals in the Regulation of Appetite Expression	283
Tonic Signals in the Regulation of Appetite Expression	283
PSYCHOLOGICAL AND BEHAVIORAL ASPECTS OF OBESITY	283
Genetics Versus Environment?	284
Obese Eating Style?	284
Underperformance of Appetite Control and Deficits in the Specific Satiety Mechanisms	285

Differences in Palatability/Hedonic Experience and Over-Responsiveness to High Fat Foods	285
Trait Hunger, Disinhibition, and Binge Eating	286
BEHAVIORAL INDICES FOR ASSESSING THE ACTION AND EFFICACY OF ANTI-OBESITY DRUGS	287
Susceptibility to Obesity and Hyperphagia	287
Structure of Feeding Behavior	288
Assessing the Effects of Drugs on Human Feeding Behavior	288
Microstructure of Human Eating Behavior: Eating Rate, Cumulative Intake Curves and Deceleration	289
MOLECULAR TARGETS FOR ANTI-OBESITY DRUGS	290
Lipase Inhibitors	290
Serotonin/Noradrenaline Reuptake Inhibitors	291
Sibutramine	291
Tesofensine	291
PSN 602	292
Selective Serotonin Receptor Ligands	292
5-HT _{2C} Receptor Agonists	292
5-HT ₆ Receptor Antagonists	293
Cannabinoid Receptor Ligands	295
Neuropeptide Receptor Ligands	295
Amylin, Glucagon, and GLP-1	295
NPY (Y2, Y4, and Y5)	296
Melanin-Concentrating Hormone	296
Peptide YY	297
SCREENING STRATEGIES FROM MOLECULAR TARGET TO INITIAL CLINICAL TRIAL	297
PROOF OF CONCEPT FOR NOVEL ANTI-OBESITY DRUGS: THE ROLE OF EXPERIMENTAL MEDICINE STUDIES TO DETERMINE DRUG EFFICACY AND SIDE-EFFECTS	299
Measurement of Anti-Obesity Drug Efficacy in Experimental Medicine Studies: The UEM Approach	299
Measurement of Anti-Obesity Drug Efficacy and CNS Side-Effects in Experimental Medicine Studies: The Emotional Test Battery Approach	300
SUMMARY	302
REFERENCES	302

INTRODUCTION

The current obesity epidemic and its severe consequences for health provide a strong rationale for developing safe and effective drugs to help manage obesity. Existing drugs have modest efficacy, and may cause clinically significant adverse effects that limit their widespread acceptance. Recent developments in the science of body weight regulation have provided a wealth of potential targets for drug development,

and many candidates are now reaching the clinical development stages, however it remains to be seen which of these will be successful. There have also been many recent developments in the assessment of altered energy balance, adiposity, and its pathophysiological consequences that give researchers a wealth of potential markers of treatment success, although it is likely that only hard clinical endpoints will eventually convince regulators and physicians that obesity treatment is worthwhile.

Despite the lack of a specific obese eating style, obesity and weight gain are associated with heightened preference for dietary fat, weakened satiety mechanisms, high disinhibition and hunger, and in some instances, binge eating. These may constitute distinct obesity behavioral phenotypes. By using models of dietary-induced obesity (DIO), food choice and satiety, and the detailed assessment of drug effects on the expression of human appetite, early indications of the efficacy of appetite-suppressing anti-obesity drugs can be gauged. How we use these models to best indicate clinical success remains to be determined.

CLINICAL ASPECTS OF OBESITY AND CARDIOMETABOLIC DISEASE

Background – Do We Need Drugs for Obesity?

There is no doubt that the world is facing a major epidemic of obesity, largely as a result of rapidly changing lifestyles, with increased availability of energy dense, palatable foods, and declining levels of physical activity being widely recognized as the key culprits.¹ The major health consequences of this obesity epidemic are now recognized to be significant. A very wide range of obesity-related co-morbidities are becoming more prevalent in the population, and this will have serious consequences for the health of these individuals, and for the health care economies that will have to fund the costs of this increased burden of disease. The greatest contributor to this is undoubtedly type 2 diabetes,² closely followed by the related problems of dyslipidemia and hypertension which lead to greater risk of macrovascular diseases, such as myocardial infarction, stroke, and peripheral vascular disease. Together with obesity, these make up the components of the metabolic syndrome which is now thought to affect about 25% of the population in the United States and many other developed nations.³ Other consequences of obesity are also important – these include increased risk of several gastrointestinal and genitourinary cancers, obstructive sleep apnea, osteoarthritis, back pain, infertility, congenital abnormalities and mood disorders, especially depression.

Given this significant disease burden, it is not surprising that attempts are being made both to address the causes of the epidemic at a population level through public health initiatives,⁴ and to provide guidance to clinicians and health care professionals who are seeking effective ways to intervene to help individual patients lose weight. At present the most effective approaches are surgical, but these are generally reserved for the most severely obese patients and still carry significant risk in terms of morbidity and to some extent mortality. Various dietary approaches, with and without physical

activity programs have been shown to have limited success, with even the most comprehensive programs only producing a mean weight loss of about 4 kg after 2 years of intervention.^{5,6} This has led to a genuine clinical need for pharmacological treatments that at present sit between lifestyle approaches and surgery in terms of their clinical effectiveness.

Current Drugs for Obesity and Their Limitations

Orlistat (Xenical®/Alli®) is an intestinal lipase inhibitor. It is not systemically absorbed, but acts within the gut lumen to block the digestion of approximately 30% of ingested dietary fat; for a person on a typical Western diet containing 40% energy from fat, this will result in an energy loss of about 200 kcal per day. Orlistat is licensed for the treatment of obesity in patients with a body mass index, BMI > 30 kg/m² (or >28 kg/m² if co-morbidities, such as diabetes, hypertension, or dyslipidemia are present). The usual dose is 120 mg three times daily with meals. It should only be used for longer than 3 months if a 5% weight loss has been achieved. Possible side-effects include loose, fatty stools, oily spotting, and occasionally fecal incontinence. Small falls in circulating concentrations of fat-soluble vitamins have also been observed.⁷ Clinical trials have lasted for up to 4 years, and have consistently shown greater weight loss with orlistat than placebo (mean placebo-subtracted weight loss = 3.5 kg after 2 years of treatment).^{8,9} Weight loss is slightly less in those patients with type 2 diabetes.¹⁰ In general a broad range of cardiovascular risk factors are improved with orlistat treatment, including LDL cholesterol, blood pressure, and blood glucose. In patients with impaired glucose tolerance, orlistat has been shown to reduce the risk of progression to overt diabetes by 46% in a subgroup of patients in a larger, 4-year study.⁸ A low dose preparation (60 mg three times daily) of orlistat with about 80% of the efficacy of the standard preparation has recently been licensed for over-the-counter sale in the United States and Europe.

Sibutramine (Reductil®/Meridia®) is a centrally acting serotonin and noradrenaline reuptake inhibitor. It acts to increase satiety, and may also have a modest effect to reduce the fall in metabolic rate seen after weight loss. It is licensed for up to 12 months use for patients with a BMI > 30 kg/m² (or >27 kg/m² if co-morbidities are present). The starting dose is 10 mg daily. This can be increased to 15 mg after 1 month if 2 kg weight loss has not been achieved; the drug should be discontinued at 2 months if 2 kg weight loss has not been reached. It should only be used longer than 3 months if a 5% weight loss has been achieved. Side-effects include constipation, dry mouth, tachycardia, and sometimes a rise in blood pressure. Blood pressure and pulse rate should be monitored before starting therapy with sibutramine; the drug should not be used if blood pressure exceeds 145/90 mmHg, and discontinued if the systolic or diastolic blood pressure rises by more than 10 mmHg or if the pulse rises by more than 10 beats per minute on two consecutive visits. Monitoring of blood pressure and pulse should be every 2 weeks for the first 3 months of treatment, monthly for the second 3 months, and 3 monthly thereafter. It is also important to note that there are a number of contraindications for sibutramine, including congestive cardiac failure and concomitant use with antidepressants. The average placebo-subtracted weight loss in clinical trials (where all patients received lifestyle advice) was 5.3 kg after 12 months, compared to 0.5 kg for placebo.¹¹ Slightly less weight loss is seen in patients with

pre-existing diabetes.¹² Whilst sibutramine can improve lipid profiles, specifically increasing HDL cholesterol and lowering triglycerides it may, in some patients cause a rise in blood pressure, and often a small (1–3 beats per minute) increase in heart rate.¹³ This effect on blood pressure has been the cause of some concern, but in general only affects a small percentage of patients.¹⁴

Rimonabant (Acomplia®) is an antagonist at the cannabinoid-1 (CB1) receptor and has recently been licensed in the European Union for the treatment of obesity in patients with a BMI > 30 kg/m² (or >27 kg/m² if co-morbidities are present). The dose is 20 mg daily. The most common side-effects (>5% patients in trials) were nausea, dizziness, diarrhea, anxiety, upper respiratory tract infection, nasopharyngitis, influenza, pain in extremities and arthralgia. The side-effects that have received most attention relate to alterations in mood and an increased risk of anxiety and depressive disorders, including suicidality. This led to a US Food and Drug Administration (FDA) advisory committee voting against approval of rimonabant in the United States until longer term safety and efficacy data are available, despite good evidence of clinical effectiveness in clinical trials, with a mean placebo-subtracted weight loss of 5.4 kg, evidence of efficacy in type 2 diabetes and dyslipidemia, and improvements across the full range of cardiovascular risk factors, including lipids, blood pressure, and diabetes control, some of which may be due to peripheral metabolic effects that may be independent of weight loss.^{15–18}

Other Drugs – Withdrawn or No Longer Recommended for Routine Clinical Use

There are many drugs that were originally approved in the 1950s and 1960s for the treatment of obesity, at a time when much less stringent regulations were in place than at present for the licensing of such agents. These included centrally acting amines such as dexamphetamine and metamphetamine (now withdrawn), phentermine and diethylpropion (which remain available in some countries, but are not recommended for routine use). These agents, whilst effective for short-term weight loss, have significant cardiovascular central nervous system (CNS) and side-effects, including tachycardia, palpitations, sleep disturbance, anxiety, and a potential for dependence, and in general, their risk-benefit ratio is considered unfavorable. The second generation of drugs was based on the serotonin system, and included mazindol, fenfluramine, and dexfenfluramine.¹⁹ The latter two were withdrawn in 1997, following reports of cardiac valve abnormalities, particularly when the drugs were used in combination with phentermine.²⁰ Thyroxine and diuretics have been used in some clinical settings, but have no place in the management of obesity.

The Need for New Drugs

Given the increasing burden of disease associated with obesity, and steadily increasing evidence on the benefits of weight loss, there is a clear medical need for effective treatment. However the limitations of existing drugs, as described above in terms of limited efficacy and adverse effects, makes development of new alternatives an important scientific goal. Achieving this goal requires a concerted effort to fully understand the

biology of human energy balance, a complex biological system that is sensitive to psychological and societal influences, as well as biological feedback mechanisms. The regulatory hurdles are also now set very high, such that any potential new drug must pass stringent tests of both efficacy and safety before it can be made available to patients. The remainder of this chapter will describe current understanding of energy balance regulation, how changes can be detected and monitored, the role of psychobiological factors, and their assessment, and finally, a description of current targets and the regulatory steps required before a new drug for obesity can be approved.

BIOLOGY AND GENETICS OF ENERGY REGULATION AND IMPLICATIONS FOR OBESITY

Energy balance is very tightly regulated over the adult lifetime of an organism. This is a particularly remarkable feat given the variations in energy intake and expenditure that may occur on a day to day basis in most adult humans. For example, for a person with energy requirements of 2000 kcal per day, a 10 kg weight gain over 40 years would equate to an error of only 0.0024% in overall energy balance. It has been essential from an evolutionary perspective for humans to maintain sufficient energy stores to cover immediate and medium term future metabolic requirements, to deal with times of shortage, and increased requirements because of changes in temperature, physical activity, and the increased nutritional demands (on the female) of carrying a fetus to term and providing for the child's early nutritional needs. Short-term energy stores exist in the form of muscle and liver glycogen, and medium and long-term energy stores as lipid, stored in adipose tissue.

A complex regulatory system has evolved to preserve energy balance. The key components of this system are the energy stores, the nutrient sensing, neural and hormonal pathways that signal whether or not there is sufficient energy to meet immediate and future needs, and the CNS components that integrate these signals and determine energy intake and help regulate metabolism and energy expenditure (Figure 8.1). Two important points about these systems are that firstly, whilst there are strong evolutionary pressures to increase food intake and conserve energy, those that might regulate weight to a healthy level and protect against chronic disease are much weaker, as many of these conditions develop beyond reproductive ages. Secondly, the capacity of adipose tissue to expand and store energy is very large, such that a very high positive energy balance is possible.

Short-Term (Episodic) Signals

The short-term, episodic signals regulating energy intake are generally those that signal either the onset or the termination of a meal.

Meal Onset

There is some evidence that small decrements in blood glucose may trigger meal onset, although this hypothesis has not been widely accepted.²¹ Most recent interest has focused on the hormone ghrelin. Ghrelin was initially identified as the ligand for

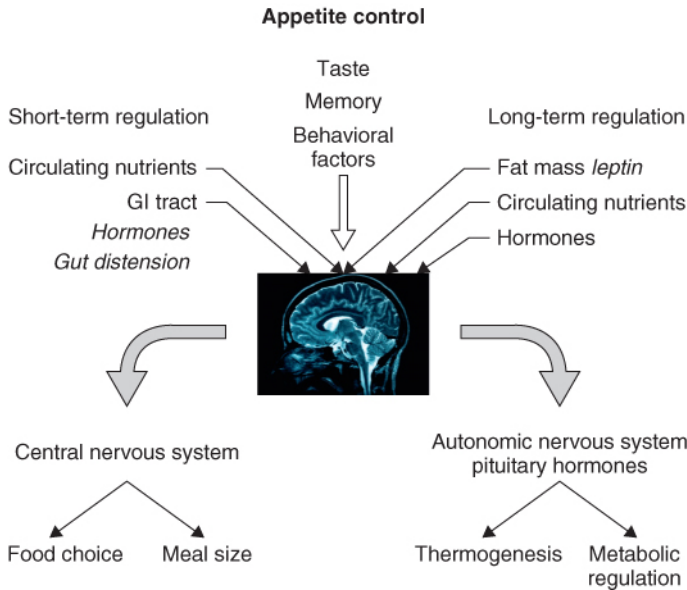


Figure 8.1 Regulation of appetite control

an orphan growth hormone secretagogue receptor (GHS-1), but the observation that it was predominantly expressed in the stomach, and that administration produced a robust increase in food intake in animals and humans, led to its identification as an important regulator of food intake.²²⁻²⁴ Circulating ghrelin concentrations rise in anticipation of meals, even in the absence of external time cues, suggesting it may be a meal initiation signal.²⁵ Ghrelin concentrations are reduced in obesity, and restored by weight loss, suggesting it is unlikely to be a major etiological factor in most obesity,²⁶ although the observation of increased ghrelin concentrations in Prader-Willi syndrome, one of the commonest monogenic obesity syndromes is intriguing.²⁷

Meal Termination

Many gut-derived hormones have been implicated in the process of post-meal satiation; the first of these to be identified was cholecystokinin (CCK), which has been shown to reduce food intake in a number of studies in rodents and humans.^{28,29} This effect occurs via both central and peripherally located receptors. Agonist drugs at the CCK-A receptor have been developed,³⁰ but none have proceeded beyond Phase II clinical studies. More recently identified physiological peripheral satiety signals include peptide YY 3-36 (PYY), and two preproglucagon-derived peptides, glucagon-like peptide 1 (7-36) amide (GLP-1) and oxyntomodulin, both of which act via the GLP-1 receptor.³¹⁻³³ One long-acting peptide agonist at the GLP-1 receptor has already entered clinical use as a treatment for diabetes mellitus (Exenatide®), and this agent both stimulates insulin secretion and results in modest weight loss.³⁴ It remains to be

seen whether small molecule agonists or long-acting peptide analogs of PYY or oxyntomodulin will prove to be sufficiently potent for clinical use.

Thermogenesis

Neural signals from the CNS to the periphery that regulate thermogenesis can also be considered short-term signals that are reacting to a change or threatened change in the organism's energy balance. The most important signal here is the sympathetic outflow to brown adipose tissue. This is activated after meals and in the cold (to generate heat) and its output is reduced under conditions of energy restriction. This system is especially important in smaller organisms, such as rodents, which have a large surface area to body mass ratio, but they do probably only have a limited role in adult humans; it has proven difficult to identify agents that are sufficiently selective to be useful drugs in humans,³⁵ and the limited capacity of adults to increase thermogenesis makes this a relatively unattractive option, although many existing drugs that decrease energy intake have a modest effect to increase thermogenesis, as these two biological processes appear to be closely coupled.³⁶

Long-Term (Tonic) Signals

The most studied long-term signal is undoubtedly leptin. Leptin is the gene product of the leptin gene, a defect in which causes obesity in the ob/ob mouse.³⁷ Leptin is produced almost exclusively in adipose tissue, and acts via the blood stream at sites in the hypothalamus to reduce energy intake. Soon after the discovery of leptin, its receptor was also cloned; mutations in the leptin receptor were found to be responsible for obesity in the db/db mouse and the Zucker fatty rat.^{38,39} In rodents and humans without mutations in the leptin receptor, circulating leptin concentrations are proportional to fat mass, so leptin deficiency is unlikely to account for most human obesity, and clinical trials in obese humans have shown leptin to be ineffective at reducing body weight.⁴⁰ Leptin is however of undoubted biological importance in body weight regulation in humans - Farooqi and colleagues have described two children with severe early onset obesity associated with a homozygous mutation in the leptin gene resulting in an absence of functional leptin, and a dramatic near normalization of body weight with recombinant leptin therapy.^{41,42} These children also have abnormalities in gonadotrophic and immune function, consistent with earlier observations made in leptin-deficient rodents. Heterozygotes have also been found, and tend to lower leptin and have a BMI higher than those with two normal copies of the leptin gene. Rare cases of leptin receptor mutations have also been described; unfortunately these are not amenable to treatment.⁴³

Insulin can also be considered a tonic signal as it is taken up into the cerebrospinal fluid (CSF) through an active transport mechanism and acts on central appetite regulating pathways to reduce food intake, interacting with leptin signaling at several levels.⁴⁴ In baboons, CSF insulin appears to mirror long-term changes in energy balance, further supporting its potential role.⁴⁵ It has been more difficult to study effects of insulin in humans, but some insulin analogs in clinical use for diabetes treatment appear to cause less weight gain than conventional insulin, possibly because of increased CNS access.

CNS Integrating Pathways

Most of the pathways described above converge on the hypothalamus, which integrates these signals to determine eating behavior and to regulate peripheral energy expenditure. However these pathways can be overridden by higher centers and the social and psychological context is of great importance when trying to understand energy balance regulation fully. The hypothalamus has several distinct clusters of neurons that are interconnected and link with brainstem afferent neurons that receive peripheral input from the vagus and direct contact with the blood, it also contains specialized areas that are considered “outside” the blood brain barrier and can therefore directly sense peripheral concentrations of nutrients. It is also in close proximity and has direct and indirect links with the CSF. Bilateral links are also present with higher centers, which may be able to modulate the final effects of these complex signals. The hypothalamus alone contains over 50 neurotransmitters and other molecules that may affect energy intake and/or energy expenditure, and although many of the major pathways are now well characterized, current understanding of the role of the hypothalamus in energy regulation is incomplete.

Major hypothalamic pathways that are regulated by leptin include neurons in the arcuate nucleus that synthesize neuropeptide Y (NPY) or Agouti-related peptide (AGRP), both of which increase food intake and decrease energy expenditure and are suppressed by leptin, and neurons that synthesize proopiomelanocortin (POMC) and cocaine and amphetamine-related transcript (CART), which decrease food intake and increase energy expenditure and are activated by leptin.⁴⁶ These pathways have mainly been identified by the study of rodents, particularly those that develop obesity such as the Agouti mouse, which overexpresses Agouti, an antagonist at the melanocortin 4 (MC4) receptor. Interestingly, the commonest monogenic form of early onset obesity occurs as a result of mutations in the MC4 receptor, which is activated by POMC the products α and β melanocyte stimulating hormone (MSH), and other defects in this pathway, including prohormone convertase 1. Defects in POMC itself have also been described, again showing close parallels between animal models and human disease.^{47,48} Many of the other peripheral signals also converge on these key set of pathways; for example PYY is thought to mainly act by activation of the Y2 receptor which decreases NPY secretion from the arcuate nucleus, and ghrelin may also act via neurons in the arcuate nucleus, where there is a high density of the GHS receptor.^{32,49}

The monoamine neurotransmitters, noradrenaline, serotonin, and dopamine are all implicated in appetite regulation, and have been found to interact with both leptin dependent and leptin independent pathways in the brainstem and hypothalamus.⁵⁰ Many existing and potential drugs act by modulation of these systems, but the potential for “off target” effects has proved problematic, with only phentermine, diethylpropion, and sibutramine remaining available for clinical use, and with concerns about abuse potential and cardiovascular adverse effects and a remarkable paucity of long-term safety and efficacy data limiting the use of phentermine and diethylpropion to short-term use only.¹ New developments, focusing on the serotonin 5-HT_{1A}, 5-HT_{2C}, and

¹ Please refer to Rocha *et al.*, Development of medications for heroin and cocaine addiction and regulatory aspects of abuse liability testing, in this Volume for further discussion of regulatory aspects of abuse potential of drugs.

5-HT₆ receptors that are specifically involved in appetite control may prove to be of value in the future (see below).⁵¹⁻⁵⁴

The endocannabinoid system is relatively recently characterized, but has already resulted in the development of the CB1 receptor blocking drug, rimonabant, that has now been licensed in Europe and some other countries. The endocannabinoid receptors CB1 and CB2 were cloned as receptors for the active ingredient of cannabis, tetrahydrocannabinol, which is well known to increase food intake. CB1 receptors are distributed widely in the CNS and periphery, whereas CB2 receptors are only found peripherally, and are thought to be concerned with immune and nociceptive functions.⁵⁵ Endogenous ligands for the CB1 receptor are synthesized on demand from arachidonic acid and include anandamide and 2-archidonylglycerol (2-AG). They increase food intake, and their concentrations are increased in rodent models of dietary obesity and in leptin receptor mutations, suggesting a physiological role.^{56,57} Unfortunately the CB1 receptor has other roles, including effects on mood and anxiety, which is the basis for some of adverse effects seen in rimonabant clinical trials. A number of other CB1 receptor antagonists are in development (see below), but it remains to be seen if these will have significant benefits over rimonabant in terms of efficacy and adverse effect profiles.

Whilst much of the basic scientific work on the regulation of energy balance has been conducted in rodents, studies of rare obesity syndromes in humans have shown the importance of similar pathways, and many of the regulatory pathways identified so far in rodents appear to have a similar functional role in humans. Nevertheless it is essential to consider potential species differences, and conduct work in humans as well as rodents, particularly when validating potential drug targets in obesity. This can be particularly problematic when considering CNS targets, as it is often the case that the only way a target can be validated is by means of a clinical trial. It is therefore important to consider whether biomarkers or other surrogates can be used to help study the regulation of body weight, and help validate potential drug targets.

BIOMARKERS OF ENERGY REGULATION AND OBESITY

Anthropometric Measures

BMI (calculated as weight in kg/height² in meters) has been considered the standard measure of adiposity for clinical use and for epidemiological studies for many years. A considerable amount of data based on BMI have been used to show the increased morbidity and mortality associated with obesity and the WHO current definitions of obesity, still rely predominantly on BMI.¹ However use of BMI as the sole measure of fatness can classify some physically fit, muscular individuals as obese because it does not directly measure body fat or fat distribution. Other simple anthropometric measures that can be used to complement BMI, and may be better markers of some (particularly diabetes and cardiovascular) disease risk include measures of waist circumference and waist-hip ratio.⁵⁸ However these measures probably add little to disease risk estimation in people with a BMI significantly above 35 kg/m². Other more detailed measures of body composition, derived from skin-fold thickness measurements, can be accurate when used by experienced researchers, but are certainly too time

consuming for routine clinical use, and have largely been superseded by non-invasive measurement of body fat, using modern imaging technology.

Measures of Adiposity

The gold standard measures of body fatness are underwater weighing and double-labeled water techniques; the former requires specialist equipment and is an awkward technique for both subjects and researchers. Double-labeled water is expensive, and availability is limited by access to isotope.⁵⁹ The newer technique of air-displacement plethysmography (“Bod-Pod”) overcomes some of these limitations, and has been reasonably well validated against gold-standard techniques.⁶⁰ Dual beam X-ray absorptometry (DEXA) is widely available, and uses a low radiation dose (less than 10% of a standard chest X-ray). Using a three compartment model it provides an accurate estimate of lean body mass, fat mass and body water and an estimate of fat distribution. Bioimpedance techniques estimate body fatness using prediction equations from measures of body water and lean body mass derived from electrical conductivity of the body. The prediction equations and techniques are improving all the time.⁶¹ Bioimpedance methods are popular because of low cost of the equipment and ease of use, and may be of particular use in large, long-term longitudinal studies, and in clinical practice to measure changes within individuals, but limitations mean they are unlikely to be accepted as a gold standard for clinical research studies.

Most of these measures do not take into account fat distribution, which is important when assessing risk of diabetes and cardiovascular disease, so any study which wishes to assess changes in risk, should measure both change in total body fat, and use a measure of fat distribution. Measures of fat distribution should take into account both subcutaneous, and “visceral” fat – the latter may include fat that is deposited within non-adipose cells within tissues, such as muscle and liver. Subcutaneous and visceral fat area can be measured using CT or MRI scanning. Most protocols measure visceral and subcutaneous fat area from a single or multiple slices. MRI is preferred for research because it does not involve radiation exposure. Techniques that estimate visceral fat volume are also available, but remain at the experimental research stage at present.⁶² All of these techniques are of limited value in the most extremely obese individuals, who are often too heavy or are of too great girth to be scanned safely, even with modern scanners. Direct measurement of intracellular fat in tissues such as muscle and liver using MRI is of considerable research interest, but its use is currently limited to a few very specialist centers worldwide.⁶³

Leptin correlates approximately with total fat mass, and may be considered a crude biomarker reflecting this, but gender differences and wide variation between individuals for a given fat mass limits its usefulness in this regard. The recently identified hormone omentin has recently been suggested to inversely reflect visceral fat mass, but this requires further validation.^{64,65}

Measures of Energy Expenditure

The three main components of energy expenditure are the basal resting metabolic rate (RMR), the thermic effect of food, and the energy requirements of voluntary physical

activity. Accurate measurement of energy expenditure is an important biomarker, and can be used both in the study of the etiology of obesity and in the evaluation of therapy. Calorimetric methods rely on measurement of oxygen consumption and carbon dioxide production, with a correction for protein metabolism based on measurement of urinary nitrogen excretion. Whole body calorimetry in a sealed room is considered the gold standard, but requires considerable technical support and is expensive to set up and maintain; it can however be used to study subjects over a period of time, and can therefore include the effects of meals and episodes of physical activity. Indirect calorimetry using ventilated hood systems is a popular alternative, which correlates well with whole body measurements of resting energy expenditure and is useful for making short-term measurements of RMR and the thermic effect of food. Physical activity can be measured to a reasonable degree of accuracy using modern triaxial accelerometers, but these can only provide estimates of the energy expenditure.⁶⁶

The gold standard for free living individuals requires the use of doubly labeled water ($^2\text{H}_2^{18}\text{O}$), which can be used to estimate energy expenditure over periods of 3–10 days with a reasonable degree of accuracy ($\pm 4\%$).⁶⁷

Risk Factors

When evaluating the clinical effectiveness of anti-obesity drugs there is no doubt that measurement of conventional cardiovascular and metabolic disease risk factors is essential. At a minimum, evaluations should include measurements of blood pressure, fasting measurements of total, HDL and (calculated) LDL cholesterol, triglycerides, and blood glucose.

Insulin Resistance and Systemic Inflammation

Other biomarkers of CV and metabolic risk may also be measured, although their usefulness in routine clinical practice is not yet proven. Improvements in insulin resistance are expected with effective weight loss and it is helpful to demonstrate that this improves, especially as insulin resistance may precede and usually co-exists with type 2 diabetes. Several methods exist – the simplest involve measurement of fasting insulin and glucose, such as the HOMA (homeostasis model assessment) and QUICKI, but these are probably less accurate than the hyperinsulinemic euglycemic clamp or frequently sampled intravenous glucose tolerance tests.^{68,69} In general, for large clinical trials a simple fasting test will probably suffice, reserving the more sophisticated methods if it is necessary to answer a specific question; however innovative study designs are needed to convincingly demonstrate “weight loss independent” effects on insulin resistance.

Other “non-classical” risk factors such as uric acid, fibrinogen, plasminogen activator inhibitor 1 (PAI-1), C-reactive protein (CRP), tumor necrosis factor α , interleukins, adiponectin, and liver function tests (particularly alanine transferase as a measure of fatty liver) are also likely to improve with weight loss and could also be considered helpful surrogates of metabolic improvement, although recent experiences with thiazolidinediones (e.g., rosiglitazone) for diabetes, may temper enthusiasm for reliance on such surrogate outcomes.

THE PSYCHOBIOLOGY OF APPETITE EXPRESSION

Despite the complexity of the biology underpinning energy regulation, many individuals experience great difficulty controlling their own body weight. The system appears not to be able to control excess energy intake. In theory, only a small reduction in daily food intake, over time, could yield significant weight loss. However, in practice this small behavioral change is difficult to achieve for the majority of those seeking to lose weight. This suggests a specific need for pharmacological assistance to gain better control of appetite and not just produce weight loss. Underpinning the structure of feeding behavior in animals and eating behavior in humans are the numerous systems which inform the brain of the body's energy status. These signals can be classed as either episodic or tonic.^{70,71}

Episodic Signals in the Regulation of Appetite Expression

The differentiation between episodic and tonic regulatory signals has previously been described. However, it is worth considering these signals, critical to appetite regulation, from the psychological perspective. Episodic feedback is generated by signals arriving from sensory systems (from oral cavity to gut) and the detection of changes in metabolic parameters caused by ingestion. From the anticipation of intake caused by the perception of food, through the oro-sensory experience of consumption, the distension of the gut as food is swallowed, the chemo-detection of nutrients in the gut, and finally the post-ingestive effect of circulating products of digestion, these episodic signals provide a rich array of information on recent energy intake. This transient input allows the body to estimate near instantaneously what has been eaten and thereby adjust eating behavior appropriately. Deficiencies or abnormalities in episodic systems can promote over-consumption and may sustain abnormal eating behavior.^{70,71}

Tonic Signals in the Regulation of Appetite Expression

Tonic signals are derived from the conversion and storage of energy, and are responsive to deficits or excesses of energy stored in adipose tissue. In this respect they differ from episodic signals, representing a less immediate but more accurate representation of the body's energy needs. Despite their tonic nature they show circadian periodicity (i.e., some meal by meal flux). Moreover, absence of tonic inhibitory signals can cause dramatic effects on the expression of eating behavior.⁷² Thus, tonic signals are equally important in controlling the expression of eating behavior.⁷¹

From the behavioral perspective, both episodic and tonic systems contribute to the expression of eating behavior, determining when and how much is eaten. Fluctuations in both produce strong feelings of either hunger or satiety. Moreover, a deficiency in either can cause marked aberrations in the expression of eating; thus they have a common output. Where the episodic and tonic systems differ is in the nature of the input and the duration of their effects.

PSYCHOLOGICAL AND BEHAVIORAL ASPECTS OF OBESITY

The constant metabolic need for energy requires co-ordinated behavioral responses appropriate for the food environment. Given fluctuating environmental demands and

the idiosyncrasies of human nature, the fact that individuals can often maintain a fairly constant weight over prolonged periods of time suggests considerable regulatory behavior control. As leptin deficiency shows us, an intimate link between the status of energy stores and the expression of eating behavior must exist.

Genetics Versus Environment?

The rapid rise in levels of obesity has focused interest on factors such as diet, lifestyle, and the obesogenic environment. Nonetheless, a genetic component to obesity is difficult to deny.^{73,74} For genetically identical individuals the same phenotype can persist in quite different environments. However, some environments do not permit the expression of a genetic propensity to gain weight.⁷⁵ Human obesity has a strong polygenic component that is expressed in both vulnerable populations and in individuals in a permissive environment.⁷⁶

Over the last 14 years hundreds of gene polymorphisms have been linked to human obesity.⁷⁷ Whilst our understanding of genetics and the physical phenotype has improved, behavioral phenotypes have been somewhat overlooked. Genes underpinning appetite expression, that is, hunger and satiety, may be critical in explaining individual susceptibility to obesity.⁷⁸ Whether obesity can be considered less of a metabolic and more of a neurobehavioral disease⁷⁸ is currently uncertain, but behavioral traits linked to obesity constitute phenotypes worthy of examination.

The focus on metabolic rather than behavioral markers for obesity has hindered research into behavioral phenotypes, but progress has been made. For instance, Blundell *et al.*⁸⁰ have identified subpopulations of high fat consumers, either disposed or resistant to diet-induced weight gain. What differs between the two groups is not habitual diet *per se* but the expression of their eating behavior. Specifically the obese high fat consumers have a weaker satiety response to fatty meals, a preference for fat that is not diminished by satiety, a stronger hedonic attraction to palatable foods and to eating and higher trait hunger and disinhibition scores. These would all promote a positive energy balance and adiposity.

Obese Eating Style?

From the beginnings of the study of obesity, researchers have sought to define characteristic differences in eating behavior between obese and normal weight individuals accurately. Early laboratory-based observational studies tried to define a specific “obese eating style”.⁷⁹ These early studies showed that the obese had a faster eating rate (g/min), chewed each mouthful less and consumed more mouthfuls per minute.⁷⁹ However, due to the small sample sizes, differing methodologies employed, and the demand characteristics of these studies, no real agreement on what characterized “obese eating style” could be reached.

There were theoretical as well as methodological problems with these early studies. Stunkard and Kaplan⁷⁹ suggested that assumptions of homogeneity (i.e., that all obese, irrespective of weight-status, age, and gender would react in the same way) and robustness (that these eating styles would persist despite variations in eating circumstances) underpinning these studies were problematic. Despite this, Stunkard and

Kaplan also noted that some traits were commonly observed in these studies. Firstly, obese individuals often failed to demonstrate the decrease in eating rate (deceleration) that normally characterizes the end of a meal. Secondly, obese individuals, when offered a range of foods, tended to choose a greater number of differing food items during their meal, an effect that was dependent on the palatability of the food items offered.

Even with the decline in the notion of an “obese eating style,” the idea that traits, such as eating rate and responsiveness to highly palatable food, constitute risk factors for over-consumption remain.^{71,80} Once the mechanisms underpinning these traits, or behavioral phenotypes, have been identified, therapeutic approaches may be possible.

Underperformance of Appetite Control and Deficits in the Specific Satiety Mechanisms

From the earliest studies of eating rate and meal size, data have suggested that ingested food may impact less on the eating behavior of obese individuals than their lean counterparts. For instance, the normal physiological development of satiety, a deceleration in cumulative intake during a meal, is not always seen in the obese.⁸¹⁻⁸³ Thus it is possible that the obese may not experience the same satiating power of food. Certainly, weight gaining individuals have been shown to eat 1650 kJ a day more than similar sized weight stable individuals, an intake that fails to produce any proportional decrease in post-meal hunger or increase in post-meal fullness.⁸⁴ Similarly, in identical twins discordant for weight status, the obese twin reported eating significantly more food at each meal,⁸⁵ a difference not corrected for through appetite regulation. These data suggest a comparative deficiency or “underperformance” in the processes of within-meal satiation in these individuals.

A number of factors related to the episodic control of appetite could contribute to this comparatively poor satiety response. Firstly, the obese tend to consume more energy dense foods usually high in fat and/or refined sugar.^{86,87} These are foods which produce a poorer satiety response both because of their high energy density,^{88,89} and the specific deficits in the satiety response to fatty meals which characterizes obese high fat consumers.⁸⁰ Secondly, there is evidence that some obese individuals have large gastric capacities, particularly the morbidly obese and binge eaters,^{90,91} allowing the consumption of greater volumes before fullness is reached. Finally, lean/obese differences in the gastrointestinal peptide response to nutrients within the gut may constitute another physiological mechanism underpinning weakened satiation in the obese.^{71,92,93} Thus food type, gastric capacity, and physiological response to ingestion could all combine to promote continued over-consumption.

Differences in Palatability/Hedonic Experience and Over-Responsiveness to High Fat Foods

Obese/lean differences in satiety may explain some disparity in eating behavior; however, can obese individuals over consume purely because of an inherent weakness in satiety? Eating behavior is a sensory and hedonic experience; and the pleasure of consumption can overwhelm processes of satiation. Lowe and Levine⁹⁴ have argued that the food environment chronically activates the hedonic appetite system, producing a motivation to “over-eat.” Certainly, palatable food stimulates hunger⁹⁵⁻⁹⁷ and also

appears to delay fullness.⁹⁶ Indeed, Yeomans *et al.*⁹⁸ have commented that palatability exerts the strongest stimulatory effect on eating when sated.

Given the relationship between the consumption of dietary fat and obesity, it is not surprising to find experimental evidence that the obese display heightened preference for high fat foods. Food preferences in the obese and weight gainers have all been characterized by a preference for fat.^{84,99,100} Similarly, pleasantness ratings for high fat foods have been shown to correlate with percent body fat.¹⁰¹ These observations suggest that differences in hedonic experiences of certain foods may underpin obesity-promoting food choices. The hedonic capacity to enjoy high fat foods, together with a weakened response to them, constitute key behavioral risk factors, which interact to promote and sustain obesity.^{80,102}

Trait Hunger, Disinhibition, and Binge Eating

It is clear that appetite regulation goes beyond the physiological processes underpinning hunger, satiation, and satiety. In fact “uncontrolled eating” (comprising high trait hunger and disinhibition) may characterize the eating behavior of many obese individuals to a greater or lesser extent.^{103,104} The notion that the obese have a disposition to respond more to environmental stimuli to eat than to their physiological need is not a new concept. Numerous studies have shown that the obese demonstrate higher levels of trait hunger, that is, experiences such as feelings of constant/excessive hunger and over-responsiveness to the sensory characteristics of food (e.g.,^{105,106}). However, constant and provokable hunger is not the only trait associated with obesity.

Disinhibition, excessive and poorly controlled eating behavior, is also associated with adiposity.^{105,107-110} Disinhibition is associated with weight gain,¹⁰⁹ weakened satiety response to fat,⁸¹ and with dietary relapse¹¹¹ suggesting it is a key obesity-promoting behavioral characteristic. However, do hunger and disinhibition constitute obesity behavior phenotypes? Both trait hunger and disinhibition appear to have a genetic component. Provencher *et al.*¹¹² estimated generalized heritability for hunger and disinhibition to be 28% and 18% respectively. Moreover, allele variation has been shown to link behavior traits such as hunger and disinhibition with obesity and liability to gain body fat.¹¹³

An inability to control one’s weight satisfactorily lies not only at the route of obesity, but also of many eating disorders. Aberrant and disordered eating behavior, usually linked to anorexia and bulimia nervosa, is also associated with obesity. Binge eating at sub-clinical levels is very common in the obese and full blown clinical binge eating disorder (BED) is far more prevalent in the obese than other weight status populations. Moreover, the occurrence of both behavior and disorder increases in the obese population with the degree of adiposity.^{114,115-119} Binge eating is a significant clinical issue. Obese individuals with BED do appear to consume more calories than weight matched non-BED counterparts.¹²⁰

The behavior traits most linked with binge eating in the obese are disinhibition and hunger.^{116,118,121} However, whilst disinhibition and hunger serve to undermine efforts to control intake and prevent weight loss, the aberrant behavior of binge eating also serves to perpetuate the disorder itself. Binge eating undermines the physiological processes, such as gastric capacity and gut hormone release, which underpin normal

appetite expression.^{90,91,122} Normal appetite regulation and eating behavior may be partially restored with satiety-enhancing drugs.^{82,123-126}

BEHAVIORAL INDICES FOR ASSESSING THE ACTION AND EFFICACY OF ANTI-OBESITY DRUGS

Even though obesity is ultimately a matter of energy balance, that is, caloric intake exceeding energy expenditure, susceptibility is clearly linked to food choices and eating behavior. Factors such as weakened satiety, over-responsiveness to palatability, high trait hunger, high disinhibition, and binge eating are etiological and symptomological factors that require addressing during drug development.

Susceptibility to Obesity and Hyperphagia

Animal models of obesity provide important indices for the assessment of potential therapeutic effects such as changes in adiposity and body fat distribution, and in key endocrine and metabolic factors.^{127,128} Behavioral indices such as hyperphagia are necessary for assessing the potential efficacy of appetite-suppressing, anti-obesity drugs. Genetic models of obesity produce very reliable weight gain and aberrant eating behavior against which the efficacy of various drugs can be tested. Similarly, drug-induced weight gain also produces robust changes in feeding behavior and body weight. However, whilst mechanistically interesting, these models are not entirely valid representations of the human condition.²³³

Rodents, like humans, show a tendency to gain weight when exposed to a highly palatable energy dense diet and during this period they demonstrate marked hyperphagia.¹²⁹ Methods of producing Diet induced obesity (DIO) vary from adding sugar and fat to standard laboratory chow or providing separate sources of fat or sugar in addition to laboratory chow, to providing a selection of a variety of high fat and/or sugar foods in a cafeteria paradigm. The latter approaches also allow the assessment of drug effects on food choice. Some rodent strains appear more susceptible to weight gain than others, and even within groups of animals from a single strain, some animals appear to respond to the DIO exposure, whilst others do not.^{130,131} This has the potential to complicate research, but is analogous to the human condition; therefore the tendency of many investigators to solely select DIO responders for studies may not be appropriate. Critically to the treatment of the human condition, the reversal of DIO in the rodents reduces morbidity and mortality.^{128,132}

Currently, anti-obesity drugs are licensed to treat obesity and not to prevent it. Therefore, it is critical to consider whether the DIO model tests the drugs ability to prevent rather than treat obesity. Nonetheless, previously and currently licensed appetite-suppressing anti-obesity drugs have all been shown to reverse DIO and associated hyperphagia.⁸² It is important to note that in the DIO model, the effects of most drugs on daily caloric intake weaken as the study progresses, even if drug effects on body weight remain. It is difficult to say whether a loss of hyperphagia in rodents is mirrored in humans, or how it would relate to clinical efficacy, but species differences in hypophagia response may cause problems when trying to judge the clinical potential

of a drug. As so few drugs have successfully reached the clinic, it is still difficult to ascertain what type of DIO model, and which measures, best predict ultimate clinical success.²³³

Structure of Feeding Behavior

The nature of drug-induced reductions in food intake are critical in determining if a potential appetite-suppressing anti-obesity drug can progress into clinical trials. Drugs can reduce food intake in rodents and humans in a variety of ways, through the induction of nausea or malaise, or through CNS related effects such as hyperactivity or sedation. Such effects, even if secondary to drug action on mechanisms of satiety or food preference, prevent the compound being of any clinical value. The concept of using rodent behavior to determine the nature of drug-induced hypophagia is well established. For over 40 years researchers have studied drug effects on feeding and other behavior in rodents, to determine if a drug reduces food intake in a manner consistent with a selective effect on the mechanisms underpinning appetite expression.

The validity of behavior as an indicator of toxic, pathologic, or non-physiological events appears well established.^{133,134} Monitoring animal behavior, including feeding and non-feeding activities, provides a powerful bio-behavioral assay of drug action on appetite. It also avoids some problems of validity as it uses the animal's natural behavior rather than attempting to model it on the human condition. Early studies examined drug effects on food intake, frequency of eating bouts, inter-bout intervals, eating rate and meal patterning. Changes in these micro-structural indices were successfully used to discriminate between drugs enhancing satiety and those inducing hypophagia by other means.¹³⁵ One of the most detailed behavioral assays of drug action on appetite expression is the behavioral satiety sequence (BSS).^{28,136,175} The BSS examines the microstructure of rodent behavior, and the sequence consists of a stochastic progression of behavior from an initial phase of eating, through peaks of active and grooming behavior, to an eventual phase of predominately resting behavior. The BSS appears robustly related to the processes of satiation (meal termination) and the development of satiety (post-ingestive inhibition of eating) as its expression relies on the presence of a caloric load within the gut, and the stimulation of satiety factors that this gastric load produces.^{28,137} It should be noted that both current and previously licensed appetite-suppressing anti-obesity drugs, sibutramine and D-fenfluramine and a wide range of other putative satiety compounds and peptides have both been shown to preserve and enhance the BSS.^{138,139,140-142,175,205} The BSS is not only a useful screening tool, its use in conjunction with selective agonists and antagonists, has helped establish key novel anti-obesity drug targets^{138,175-177,181-182,205} (see below).

Assessing the Effects of Drugs on Human Feeding Behavior

A variety of approaches to measuring the effects of anti-obesity drugs on human food intake can be employed. Self-report measures such as food diaries, short-term recall, and food frequency questionnaires are most suited to large population samples and

not early clinical trials. Laboratory-based observation studies provide more precision and reliability at the expense of “naturalness”.¹⁴³ As with rodents, human eating behavior can be considered in terms of macrostructure, i.e., the effects of a drug on total daily caloric intake, caloric intake at each meal, macronutrient intake, meal duration, and the number of eating events occurring during the day. Such studies have been used for nearly 30 years to characterize the effects of drugs on human appetite.^{144,145} The inclusion of large *ad libitum* buffet style meals, and/or the availability of snacks throughout the day, also allows researchers to fully assess drug effects on food choice.

In human studies, researchers are able to assess the effects of drugs on subjective experiences of appetite to confirm any satiety-enhancing effect. Self-report scales have been used to determine the nature of a drug’s effect on food intake in some of the earliest human studies.¹⁴³ These rating scales initially focused on feelings of hunger and fullness, but now encapsulate other aspects of satiety such as desire to eat, prospective consumption (how much could you eat?), and satisfaction. The measures come in a variety of forms but the most widely accepted format is the visual analog scale (VAS). The VAS format presents participants with a 100 mm horizontal line anchored at each end with extremes of the sensation (e.g., “not hungry at all” and “extremely hungry”) on which to mark their feeling.¹⁴³ It is interesting to note that ratings of appetite sensations are not only predictors of energy intake but also of body weight loss.¹⁴⁶

The effect on eating behavior and appetite of drugs such as fenfluramine, D-fenfluramine, and sibutramine are well characterized in lean healthy volunteers and in the obese.¹⁴⁷⁻¹⁴⁹ As these three drugs also produce clinically significant weight loss it would appear that behavioral studies may predict clinical efficacy. In reality, behavioral studies can clearly demonstrate proof of concept but not all drugs successfully tested at this stage will ultimately possess the potential to be effective weight loss-inducing agents. For instance the selective serotonin reuptake inhibitor (SSRI) fluoxetine (Prozac®) produces clear effects on appetite and food intake in both lean and obese participants^{150,151} along with weight loss for up to 6 months of treatment, however; after that time, weight regain occurs (although it should be noted that fluoxetine went on to be used successfully for the treatment of binge eating in both bulimics and the obese).⁸² The case of fluoxetine demonstrates that behavioral studies may reliably predict weight loss over 12 or 24 weeks if not over 12 months. Therefore, as indices of performance in the next phase of clinical testing the results of these studies are still critical. Moreover, failure to determine drug effects on human eating behavior prior to Phase II weight loss trials can lead to costly failure.¹⁵²

Microstructure of Human Eating Behavior: Eating Rate, Cumulative Intake Curves and Deceleration

The effects of drugs on parameters within a meal have also been studied for nearly 30 years. Rogers and Blundell¹⁴⁴ clearly demonstrated that whilst amphetamine and fenfluramine both reduced food intake, the increase in eating rate produced by amphetamine represents the activating effects of the drug, whilst the reduction in eating behavior produced by fenfluramine represents enhanced satiety. To study eating rate, many researchers visually coded eating behavior¹⁴⁴ whilst others developed automated means of assessing intake, such as the universal eating monitor (UEM).^{153,154}

UEM curves are influenced by gender and food deprivation, as well as the composition and palatability of test meals, demonstrating that they are valid representations of the changes in appetite that occur within meals, and critically that they can be used to discriminate between factors which influence the expression of appetite.^{154,155} The UEM also appears to possess good test-retest reliability.¹⁵⁶

Cumulative intake curves may not only be useful for examining the effects of drugs and physiological states on appetite. The obese differ from the lean in the respect that they often fail to display the decelerating cumulative intake curves associated with the normal biological development of satiety.^{81,157} Failure to demonstrate a reduction in eating rate during a meal has been observed in obese children,^{158,159} in syndromes characterized by severe obesity such as Prader-Willi,¹⁶⁰ in the morbidly obese,¹⁶¹ and in obese highly restrained adults,¹⁵⁵ but not always in obese adults *per se*.^{155,162} A recent study has shown that the appetite-suppressing, anti-obesity drug sibutramine significantly slows eating rate and changes within-meal ratings of appetite consistent with satiety in the obese.⁸³ This was accompanied by a non-significant increase in frequency cumulative intake curves in the drug condition.⁸³ These data indicate that characteristic differences in the microstructure of human eating behavior may be useful in determining a drug's effects on appetite. In fact, sibutramine-induced reductions in intake were associated with clear reductions in within-meal ratings of hunger and increases in those of fullness during the meal. This is the first data directly confirming that sibutramine enhances within-meal satiation. Combining continuous measurement of intake with changes in appetite provides a powerful assay of drug action. Potentially, the use of differing within-meal appetite ratings could differentiate between drugs acting on the motivation to initiate eating episodes through mechanism of liking or wanting and from those acting on satiety, a difference traditional macro-structural approaches are unlikely to detect. Certainly, opioid receptor antagonists produce distinct effects on within-meal appetite ratings.¹⁶³

MOLECULAR TARGETS FOR ANTI-OBESITY DRUGS

As discussed in detail above, molecular targets for obesity are many and varied, ranging from modifications of current therapies, such as monoamine reuptake and lipase inhibitors, to novel neurotransmitter and neuropeptide receptors. Due to past failures and drug withdrawals (see above) the pharmaceutical industry faces an increasingly uphill task in convincing the regulatory authorities of the efficacy and, in particular, the safety of new drugs to treat obesity. In this section we consider the most interesting new molecular targets for obesity, emerging strategies that can be used by pharmaceutical companies to discover and develop compounds that act on these targets and the challenging regulatory requirements for their approval as drug therapies.

Lipase Inhibitors

Attempts have been made to develop novel lipase inhibitors that reduce body weight but have a lower propensity to cause gastrointestinal side-effects than orlistat

(see above). The most advanced such compound in development is cetilistat which Alizyme and Takeda are preparing for Phase III clinical trials. In a recently published report of a Phase II clinical trial,¹⁶⁴ cetilistat produced a significant weight loss and was well tolerated in 442 obese patients in a 12-week study. Alizyme has claimed that cetilistat and orlistat have similar efficacy but cetilistat is better tolerated and causes a lower incidence of gastrointestinal side-effects than orlistat.¹⁶⁵ The superior tolerability and side-effect profile exhibited by cetilistat has been attributed by Alizyme to differences between the molecular structures of orlistat and cetilistat. Nevertheless, as both compounds act on the same molecular mechanism to cause weight loss and the gastrointestinal side-effects are thought to be mechanism based it is difficult to understand why there should be significant differences in the side-effect profile of the two compounds but no difference in efficacy. Therefore, the outcome of the planned Phase III clinical trials with cetilistat is awaited with interest.

Serotonin/Noradrenaline Reuptake Inhibitors

Sibutramine

A number of companies have attempted to develop mixed reuptake inhibitors that retain the weight loss efficacy of sibutramine (see above) but have a reduced propensity to cause cardiovascular side-effects.

Tesofensine

Tesofensine is a dopamine, serotonin, and noradrenaline (triple) reuptake inhibitor originally developed by NeuroSearch for the treatment of Alzheimer's disease and Parkinson's disease. Development of the compound for these neurological indications was unsuccessful but significant weight loss was reported during the clinical trials in Parkinson's disease.¹⁶⁶ Hence, tesofensine is now being developed by NeuroSearch for the treatment of obesity and type 2 diabetes. In September 2007 NeuroSearch reported the outcome of a Phase IIb study with tesofensine for the treatment of obesity. Data from the study in 203 patients showed that 24-weeks' treatment with tesofensine resulted in a dose-dependent weight loss of 6.5–12%. Tesofensine was reported to have a good safety profile and was well tolerated although an increased number of adverse events (e.g., increased heart rate and blood pressure) were observed in the highest dose groups of 0.5 mg and 1.0 mg. NeuroSearch¹⁶⁷ stated that no clinically relevant cardiovascular adverse events or changes in either blood pressure or pulse were seen, according to FDA criteria. Nevertheless, in studies in Parkinson's disease decreased body weight and elevated heart rate were described as common in the 1.0 mg dosage group. Further, a sustained increase in supine systolic blood pressure was recorded in 5.7% of subjects in the combined NS 2330 groups and in no placebo subjects and a sustained increase in supine diastolic blood pressure was recorded in 2.6% of the combined NS 2330 groups and in no placebo subjects. In addition, 56.2% of NS 2330 subjects had a maximum increase in heart rate of at least 10 beats per minute as evaluated on ECGs compared to 18.8% of placebo subjects.¹⁶⁶ The results of pivotal Phase III clinical trials with tesofensine for obesity are awaited to determine whether the compound will have a superior cardiovascular risk-benefit profile compared to sibutramine.

PSN 602

Prosidion is developing compounds that combine 5-HT_{1A} receptor agonist properties with monoamine reuptake inhibition. It is proposed that the increases in heart rate and blood pressure associated with sibutramine may be prevented by adding a 5-HT_{1A} receptor agonist action to monoamine reuptake inhibition. The lead compound from this program PSN 602 is undergoing preclinical testing and was expected to enter clinical studies in 2007. However, although 5-HT_{1A} receptor agonists have been reported to decrease blood pressure in animals under certain experimental conditions¹⁶⁸ there is little or no evidence that 5-HT_{1A} receptor agonists decrease blood pressure in humans.¹⁶⁹⁻¹⁷¹ Prosidion compounds have been claimed to have demonstrated anti-obesity efficacy and superior cardiovascular safety to sibutramine in rats.^{172,173} However, given the species differences in the effects of 5-HT_{1A} receptors agonists on cardiovascular responses described above, the question of whether a combination 5-HT_{1A} receptor agonist/monoamine reuptake inhibitor will be a safe and effective obesity therapy can only be resolved by clinical studies.

Selective Serotonin Receptor Ligands

Non-selective serotonin drugs such as sibutramine and d-fenfluramine have been shown to be effective weight loss agents but their therapeutic utility is limited by cardiovascular side-effects, which in the case of d-fenfluramine led to the worldwide withdrawal of the drug from the market (see above). The serotonergic actions of sibutramine and d-fenfluramine are mediated by their ability to increase extracellular 5-HT levels and thereby act on multiple 5-HT receptors, of which 14 subtypes have been identified.¹⁷⁴ It has been proposed that if the 5-HT receptor subtype at which 5-HT acts to decrease eating can be identified and if this proved to be a different 5-HT receptor subtype to that responsible for the actions of 5-HT on cardiovascular function it may be possible to develop 5-HT drugs that cause weight loss and have an improved cardiovascular side-effect profile.¹⁷⁵⁻¹⁷⁷ During the past 10 years 5-HT_{2C} receptors and 5-HT₆ receptors have been identified as the most attractive 5-HT receptor targets for obesity as both subtypes appear to be present in high densities in areas of the brain that control eating but are present in low densities or are absent in the peripheral cardiovascular system.¹⁷⁴⁻¹⁷⁹

5-HT_{2C} Receptor Agonists

There is definitive evidence that 5-HT_{2C} receptors play a crucial role in mediating the inhibitory action of d-fenfluramine on eating. Thus, the selective 5-HT_{2C} receptor antagonist SB-242084 attenuates the hypophagic effect of both d-fenfluramine and its active metabolite d-norfenfluramine.¹⁸⁰ Furthermore, fenfluramine-induced reductions in feeding are also attenuated in 5-HT_{2C} receptor knockout mice.¹⁸¹ 1-(*m*-chlorophenyl) piperazine (mCPP) is a non-selective 5-HT_{2C} receptor agonist that produces behaviorally selective reductions in food intake in rodents;^{138,182} and humans.¹⁸⁴ The effects of mCPP on feeding in rodents are attenuated by the 5-HT_{2C} receptor antagonist SB-242084.¹⁸² Chronic administration of mCPP either subcutaneously or orally significantly attenuates body weight gain in rodents and food intake and body weight gain increase toward control values in animals withdrawn from drug

treatment.^{54,185} Similarly, when administered chronically for 14 days the compound decreases body weight in obese patients.¹⁸⁴ Furthermore, in agreement with rodent data, the non-selective 5-HT_{2C} receptor antagonist, ritanserin prevents the hypophagic effects of d-fenfluramine on food intake in human volunteers.¹⁸³

Such data provide a compelling rationale for the potential utility of selective 5-HT_{2C} receptor agonists as anti-obesity agents and therefore a number of pharmaceutical companies have initiated research programs to develop selective 5-HT_{2C} receptor agonists for the treatment of obesity.

The first selective 5-HT_{2C} receptor agonists were developed in a collaboration between Cerebrus (later Vernalis) and Roche and one of the first compounds to be reported with selectivity, especially against 5-HT_{2A} receptors, was the indoline molecule VER-3323.^{186,187,188} VER-3323 reduced food intake when administered orally, and the hypophagic effect was dose-dependently blocked by pre-treatment with selective 5-HT_{2C} receptor antagonists.¹⁸⁷ This collaboration also yielded the first selective compound, VR 1065, to progress to Phase I clinical trials.¹⁸⁹ However, this compound was subsequently withdrawn from Phase I trials, when the pharmacokinetic data in humans identified high levels of a metabolite of the drug.¹⁸⁹ Another drug discovery collaboration reported at this time was that of Biovitrum and GlaxoSmithKline. During the early stages of the program Biovitrum completed Phase II trials with the 5-HT-agonist BVT.933. It was found that BVT.933 significantly reduced body weight in patients without causing any serious side-effects. However, the compound was considered to have insufficient selectivity for the 5-HT_{2C} receptor and in 2003 development of BVT.933 was terminated and the collaborative program focused on finding more selective compounds.¹⁹⁰ Recently, this collaboration appears to have been abandoned and GSK has returned all rights to the project to Biovitrum, which, subsequently, has decided not to develop the compounds further for obesity.¹⁹¹

The most advanced 5-HT_{2C} receptor agonist in development is lorcaserin, which is being developed by Arena Pharmaceuticals and began Phase III clinical trials for obesity in North America in 2006.¹⁹² Results from a Phase IIb trial of lorcaserin demonstrated that patients who received the drug experienced significantly greater weight loss than patients on placebo.¹⁹³ Lorcaserin was reported to be well tolerated at therapeutic doses and echocardiographic assessment of over 800 patients that participated in the Phase II trials indicated no apparent adverse effects of the drug on cardiovascular measures (heart valves or pulmonary artery pressures).¹⁹³ Lorcaserin is reported to have 100-fold selectivity for the 5-HT_{2C} receptor relative to the 5-HT_{2B} receptor, but is only 15-fold selective for the 5-HT_{2C} receptor relative to the 5-HT_{2A} receptor.¹⁹³ As insufficient selectivity for the 5-HT_{2C} receptor has led to the withdrawal of previous 5-HT_{2C} receptor agonists from clinical development (e.g., BVT.933, see above) it remains to be seen whether the selectivity, efficacy, and safety profile of lorcaserin will be sufficient for the compound to achieve regulatory approval and market penetration.

5-HT₆ Receptor Antagonists

The 5-HT₆ receptor is a promising new CNS target for obesity¹⁷⁷ and a number of pharmaceutical companies are developing selective 5-HT₆ receptor ligands as potential

anti-obesity agents. Interestingly, both selective 5-HT₆ receptor agonists and antagonists are being developed for obesity by different companies (see below).

Initially, the discovery of selective 5-HT₆ receptor ligands¹⁹⁴ enabled the role of 5-HT₆ receptors in ingestive behavior to be characterized. The first selective 5-HT₆ receptor antagonist to be disclosed was Ro 04-6790.¹⁹⁵ This compound has relatively low potency at human 5-HT₆ receptors and poor brain penetration.¹⁹⁴ Nevertheless, Ro 04-6790 has proved useful in probing 5-HT₆ receptor function. Thus, Ro 04-6790 reduced food intake in rats and this effect was resistant to PCPA-induced brain 5-HT depletion indicating that the 5-HT₆ receptors involved have a post-synaptic location.¹⁹⁶ Chronic administration of Ro 04-6790 for 2 weeks significantly reduced body weight gain in rats and similarly, 5-HT₆ mRNA antisense oligonucleotides have been reported to decrease body weight gain in rats.¹⁹⁷⁻¹⁹⁹ Subsequently, Perez-Garcia and Meneses²⁰⁰ have reported that two other 5-HT₆ receptor antagonists, SB-357134 and SB-399885, also decreased food intake in rats.

Somewhat surprisingly, given the effects of 5-HT₆ receptor blockade described above, Esteve is developing selective 5-HT₆ receptor agonists for obesity and have described the effects of E-6837 which *in vitro* exhibits partial 5-HT₆ receptor agonist properties in rat cell lines and full 5-HT₆ receptor agonist properties in human cell lines.^{179,201} Recently, 4-week treatment with E-6837 was reported to decrease food intake and body weight in rats with DIO. E-6837-induced weight loss was mediated by a decrease in fat mass, with a concomitant reduction in plasma leptin.¹⁷⁹

Biovitrum is developing a 5HT₆ receptor antagonist for obesity and initially disclosed pre-clinical studies with BVT.5182.²⁰² BVT.5182 was reported to decrease food intake and body weight when administered orally to mice with DIO and analysis of meal patterns appeared to indicate that the compound reduced food intake via the enhancement of satiety.²⁰² Interestingly, Caldirola²⁰² also reported that the effect of a 5-HT₆ receptor antagonist on food intake in mice was potentiated by treatment with a 5-HT_{2C} receptor agonist.

Biovitrum disclosed the selection of a 5-HT₆ receptor antagonist clinical development candidate, BVT.74316, in June 2005. BVT.74316 has been reported to decrease food intake and reduce body weight and body fat mass in both short and long-term studies in animals.²⁰³ The compound began Phase I clinical trials in healthy volunteers in August 2006.²⁰³

EPIX Pharmaceuticals is also developing a 5HT₆ receptor antagonist for obesity and recently reported results from a Phase Ib clinical trial of their development candidate PRX-07034.²⁰⁴ In this double-blind, placebo-controlled trial of 21 obese participants PRX-07034, at a dose of 600mg twice-daily for 28 days, lost a mean of 0.45 kg while participants on placebo gained 1.37 kg. Treatment with PRX-07034 was associated with a significant reduction in plasma leptin levels. After 42 days, the 28-day dosing period and a 14-day follow-up period, participants on PRX-07034 lost a mean of 0.26 kg compared to a mean gain of 1.25 kg in the placebo group. However, there was evidence of QT prolongation in the ECG of participants who received PRX-07034 and therefore further development of the drug is expected to be conducted using the R-enantiomer because EPIX believes, based on preclinical data, that the S-enantiomer is predominantly responsible for the QT prolongation.²⁰⁴

Cannabinoid Receptor Ligands

Rimonabant is a CB1 receptor antagonist that has recently been licensed in Europe for the treatment of obesity (see above). The potential psychiatric side-effects of rimonabant (alterations in mood and an increased risk of anxiety and depressive disorders, including suicidality) have recently received much attention and led to an FDA advisory committee voting against approval of the drug in the United States until longer term safety and efficacy data are available. A number of companies are developing CB1 receptor antagonists for obesity and their principal objective is retain the weight loss efficacy of rimonabant but have a reduced propensity to cause psychiatric side-effects. The most advanced CB1 receptor antagonists in development are taranabant (Merck) and CP-945,598 (Pfizer) both of which are undergoing Phase III clinical trials with NDA applications anticipated in 2008–2009. In addition, the CB1 receptor antagonists AVE 1625 (Sanofi-Aventis) and SLV 319 (BMS/Solvay) are both in Phase II clinical trials.

As the psychiatric side-effects of CB1 receptor antagonists appear to be mechanism based it remains to be seen whether the objective of retaining weight loss efficacy with a reduced risk of psychiatric side-effects can be achieved. Clearly, however, it would be prudent to assess the effects of novel CB1 receptor antagonists on both eating behavior and mood at an early stage of clinical development to minimize the risk of failure at the stage of regulatory approval (see discussion below on experimental medicine approaches to this problem).

Neuropeptide Receptor Ligands

A large number of neuropeptide receptors have been explored as potential targets for novel drugs to treat obesity. To date, however, clinical success has been limited and a neuropeptide ligand has yet to be approved to treat obesity. For example there was considerable interest in the development of CCK agonists to treat obesity based on evidence that CCK acted as a satiety factor.²⁰⁵ Thus, GlaxoSmithKline were developing the non-peptide CCK-A agonist GW-181771 for obesity but development was discontinued due to lack of efficacy in Phase II clinical trials.²³⁵

Nevertheless, the neuropeptide approach appears to hold considerable promise and several neuropeptide ligands that are currently in clinical development are considered below.

Amylin, Glucagon, and GLP-1

Pramlintide (pramlintide acetate, Symlin®, Amylin Pharmaceuticals) and exenatide (Byetta®, Amylin Pharmaceuticals, and Lilly) are injectable drugs that were approved in 2005 for the treatment of diabetes. Pramlintide is approved for patients with Type 1 and Type 2 diabetes and is a synthetic analog of human amylin (a pancreatic β -cell hormone) that acts in conjunction with insulin to delay gastric emptying and inhibit the release of glucagon. Exenatide is a GLP-1 mimetic that has multiple mechanisms for lowering glucose levels, including the enhancement of insulin secretion and is indicated for use in patients with Type 2 diabetes. Clinical trials have shown that both

drugs reduce fasting plasma glucose levels and body weight.²⁰⁶ Novo Nordisk have a GLP-1 analog, liraglutide that has completed Phase II trials in diabetes, and is also reported to result in weight loss - it remains to be seen whether they will pursue and anti-obesity indication for this agent. Oxyntomodulin, another product of the proglucagon gene, most likely acts via the GLP-1 receptor, and has been found to reduce food intake in acute studies; further Phase II trials are underway.³³

Amylin has pramlintide in clinical development for the treatment of obesity and in 2004 reported results from a Phase II study in obese subjects evaluating the safety and tolerability of the drug. In the study, obese subjects were able to tolerate higher doses of pramlintide than those previously studied in diabetes trials, and achieved clinically and statistically significant weight loss. In 2006, Amylin reported data from a Phase II study demonstrating that patients completing 52 weeks of pramlintide therapy experienced a 7-8% mean body weight reduction (depending upon dose) compared to a 1% reduction in patients receiving placebo.

A clinical study of pramlintide in combination with phentermine and sibutramine is currently underway. This Phase IIb study is designed to replicate preclinical data showing that pramlintide added to an oral obesity agent produced additive weight loss in animals and results of this study are expected in 2007.²³¹

NPY (Y2, Y4, and Y5)

NPY is a heterogeneously distributed neuropeptide that elicits its physiological effects by an action on six different receptor subtypes (Y1-Y6). NPY stimulates food intake, inhibits energy expenditure, and increases body weight by activating Y1 and Y5 receptors in the hypothalamus.²⁰⁷ Based on these observations, several companies have attempted to develop neuropeptide Y2, Y4, and Y5 receptor ligands as potential anti-obesity agents.

Shionogi & Co is developing S-2367, a selective Y5 receptor antagonist, for obesity. In pre-clinical studies S-2367 increased energy consumption, suppressed visceral fat accumulation, and improved blood glucose and serum lipid levels. Shionogi has successfully completed Phase IIa proof-of-concept studies with S-2367 and Phase IIb studies are currently underway in the United States (1500 patients in two studies). Patient enrollment was initiated in March 2007 and is expected to be completed by year end. An interim analysis of the data was scheduled for March 2008.²³⁸

7TM Pharma is developing obinipitide, a dual Y2-Y4 agonist and TM30339 a selective Y4 agonist for obesity. Recently 7TM Pharma disclosed positive results from a Phase I/II clinical study with obinipitide.²⁰⁸ The study was a double-blind, placebo-controlled dose-range finding study in obese patients to evaluate the effects of obinipitide on food intake. At present 7TM Pharma is examining the effects of obinipitide on weight loss in a 28 day Phase II study in obese patients with results expected in the first quarter of 2008.

7TM Pharma has also recently initiated a Phase I/II clinical trial with TM30339, a selective Y4 agonist for obesity.²⁰⁹

Melanin-Concentrating Hormone

Melanin-concentrating hormone (MCH) has been implicated in the control of feeding behavior and energy homeostasis. MCH stimulates food intake in rodents and deletion of MCH or the MCH-1 receptor gene decreases body weight whereas over-production

of MCH increases weight gain.²¹⁰ Blockade of MCH-1 receptors in rodents abolishes MCH-induced feeding and promotes hypophagia and weight loss.²¹¹⁻²¹⁴

Neurogen is developing MCH-1 receptor antagonists for the treatment of obesity. In May 2007, Neurogen reported the results of initial Phase I studies in 71 male and female participants with an MCH-1 receptor antagonist development candidate NGD-4715. NGD-4715 was reported to be safe and well tolerated at a broad range of doses.²³⁷ Neurogen is now planning a multiple ascending dose study in healthy volunteers and then plan to proceed into a Phase II proof-of-concept study in obese patients.

Peptide YY

Peptide YY (PYY) 3-36 is one of the two main endogenous forms of PYY, a hormone released in endocrine cells in the human small intestine after a meal.²¹⁵ Infusion of PYY 3-36 has been reported to reduce hunger and food intake in obese volunteers.²¹⁵ As PYY is a protein, initial clinical development has focused on PYY delivery by injection (Amylin) and nasal spray (Nastech).

Amylin is developing injectable AC162352, a synthetic analog of human PYY 3-36 for obesity. Subcutaneous injection of AC162352 decreased appetite and increased satiety in obese individuals.²¹⁶

Nastech Pharmaceuticals is developing a PYY 3-36 nasal spray for obesity and is currently conducting a dose ranging study to evaluate its effects on appetite and food intake in obese participants. The objective of the study is to identify appropriate doses for evaluation in a long-term Phase II efficacy and safety trial.²¹⁷

SCREENING STRATEGIES FROM MOLECULAR TARGET TO INITIAL CLINICAL TRIAL

There are a number of recognized steps used by most pharmaceutical companies to establish, validate, and conduct a drug discovery program for obesity. Many programs will begin with the identification and validation of a novel molecular target from the human genome; others will be initiated as “me too” projects when a competitor company provides initial validation of a novel target. Important considerations in the initiation of a drug discovery program are the availability of, or the potential to discover, a medicinal chemistry starting point from which to derive lead compounds (ideally that are small drug-like molecules) that act selectively on the molecular target. Once a chemical lead has been identified an *in vitro* and *in vivo* biological screening cascade will be established and validated. The screening cascade will be used to derive structure-activity relationships and to guide the medicinal chemistry required to identify biologically active lead compounds for clinical development. An example of a screening strategy that could be used for discovery of selective 5-HT_{2C} receptor agonists is illustrated in Figure 8.2.

Initial screening of compounds submitted from the medicinal chemistry program would be carried out in high throughput radioligand binding and functional (measurement of changes in intracellular calcium caused by receptor activation using a fluorescence imaging plate reader, FLIPR) assays. Active compounds that achieved initial

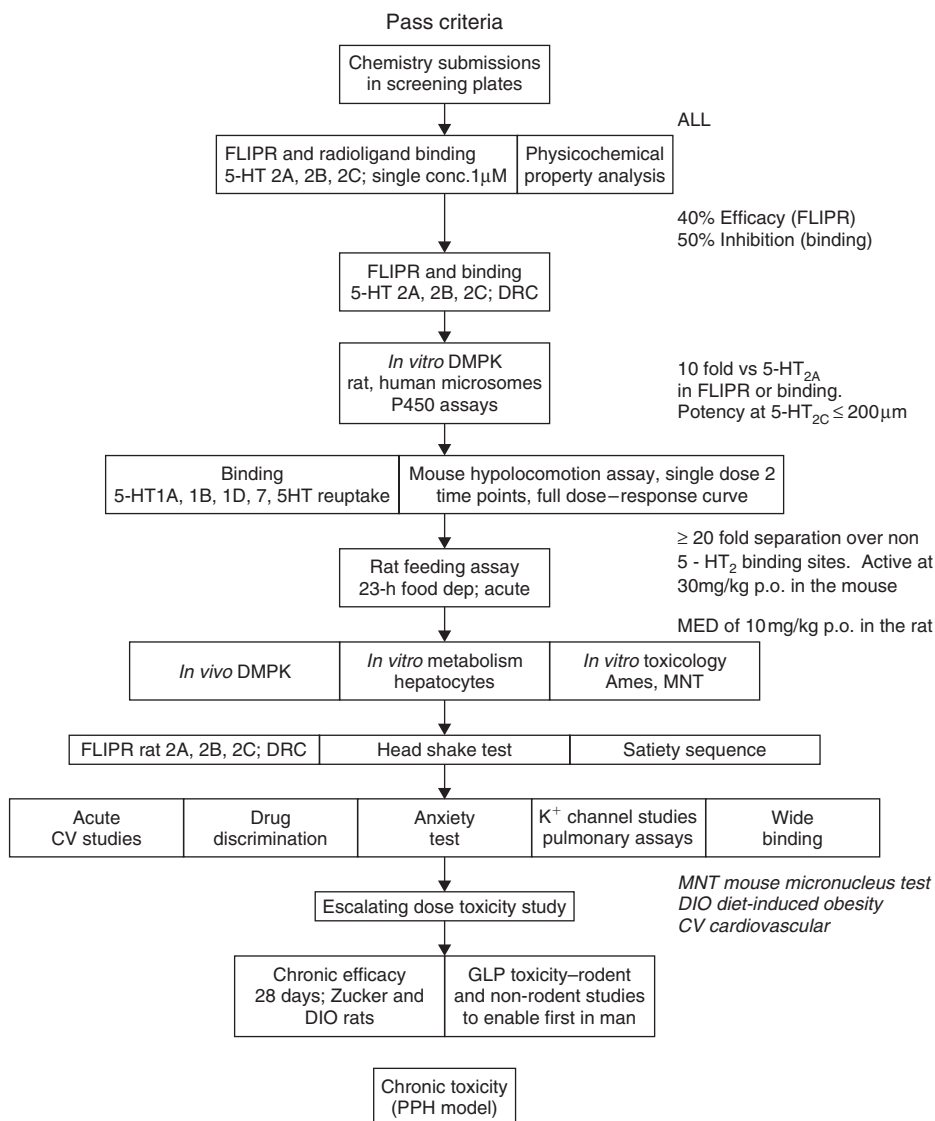


Figure 8.2 Example of a screening cascade for a 5-HT_{2C} receptor agonist anti-obesity drug discovery program

cut-off criteria would move on to dose-response (DRC) assays in radioligand binding and *in vitro* and *in vivo* assessment of drug metabolism and pharmacokinetic (DMPK) properties using liver microsomes.

Successful compounds move on to selectivity screening in radioligand binding assays and to initial *in vivo* efficacy assays using rodent motor responses.

Active compounds are next assessed for efficacy *in vivo* in simple rodent feeding assays and, if successful, their *in vivo* DMPK and *in vitro* toxicology properties are established. Compounds that pass at this stage are examined in a range of increasingly

complex rodent behavioral assays to assess efficacy (after both acute and chronic dosing) and side-effects. Success or failure in these assays will determine whether a compound is selected as a development candidate and submitted for the GLP toxicology studies required to enable Phase I clinical trials in man.ⁱⁱ

Screening strategies that have incorporated early *in vitro* and *in vivo* DMPK assays have been successful in many companies in reducing the number of clinical development failures due to poor bioavailability and pharmacokinetic properties.²¹⁸ Currently, the principal cause of failure in clinical development is efficacy and this is a particular problem for CNS targets where animal models have poor predictive validity.²¹⁸ Hence there is an urgent need to identify improved methods to reduce attrition in clinical development and experimental (or translational) medicine is a promising approach to this problem (see below).

PROOF OF CONCEPT FOR NOVEL ANTI-OBESITY DRUGS: THE ROLE OF EXPERIMENTAL MEDICINE STUDIES TO DETERMINE DRUG EFFICACY AND SIDE-EFFECTS

Obesity is currently one of the most active areas of research and development in the pharmaceutical industry, and many novel neurotransmitter and neuropeptide targets are being explored (see above). Approval of a new anti-obesity drug by regulatory authorities such as the FDA and the European Medicines Agency (EMA) requires efficacy to be demonstrated in clinical trials over a 2-year treatment period. Inevitably, many late phase drug candidates fail and each failure can cost companies hundreds of millions of dollars. As outlined above, the principal cause of failure in clinical development is efficacy and this is a particular problem for CNS targets where animal models have poor predictive validity.²¹⁸ Therefore, there is an urgent need for improved experimental medicine methods for early and accurate identification of the potential efficacy of anti-obesity drug candidates. Similarly, it is clear from the progress of recent regulatory applications such as that of rimonabant (see above) that a comprehensive CNS side-effects package will be equally, if not more, important as efficacy measures in an NDA submission. Therefore, incorporation of a CNS side-effect battery in early experimental medicine efficacy studies will be valuable as it may be possible to define a therapeutic window where there are significant drug effects on food intake but minimal CNS adverse effects.

Measurement of Anti-Obesity Drug Efficacy in Experimental Medicine Studies: The UEM Approach

The effect of anti-obesity drugs on the pattern and structure (microstructure) of human eating behavior appears likely to be critical to their efficacy (see above). Most

ⁱⁱ Please refer to McEvoy and Freudenreich, Issues in the design and conductance of clinical trials, in Volume 1, Psychiatric disorders for further discussion of development strategies following the selection of a drug candidate from preclinical drug discovery programs.

if not all potential anti-obesity drugs, however, have undergone Phase III clinical trials without detailed examination of their effect on human eating patterns in experimental medicine studies. The effects of a drug on the microstructure of eating behavior (cumulative intake, eating rate, appetite, and satiety) can provide an important measure of potential efficacy, in addition to shedding light on mechanism of action and possible side-effects (see above and below).

To measure the microstructure of eating, automated methods of assessing intake have been established that generate cumulative intake curves, from which within-meal changes in eating rate can be identified. The UEM, first reported by Kissileff and colleagues was designed to continually measure food intake through the use of hidden scales, placed underneath a participants' plate.¹⁵³ The scales could be linked to a computer to allow continuous recording of food intake and to elicit subjective ratings of appetite and satiety from participants at regular intervals during a meal.^{219,220}

Despite the sensitivity of UEM measures, the microstructure of eating behavior has not been routinely used as an experimental medicine assay for potential anti-obesity drugs. Recently, we completed a study to demonstrate that UEM-derived measures of meal intake can provide a valuable measure of the potential efficacy of anti-obesity drugs.^{83,234} Sibutramine was used as a reference standard to establish the utility of within-meal analyses of eating behavior. Previous studies had used UEM equipment to measure food intake in volunteers after sibutramine treatment,¹⁶² but had not used the UEM to investigate the effect of the drug on the microstructure of human eating behavior. The study was an outpatient, randomized, double-blind, placebo-controlled crossover trial in 30 obese female participants and examined the effects of two doses of sibutramine (10 mg and 15 mg/day for 7 days) on the microstructure of eating behavior. The results provided the most complete characterization of the anti-obesity effects of sibutramine to date and validated new UEM measures against which novel anti-obesity drugs can be compared in subsequent studies. Sibutramine at 10 mg and 15 mg reduced food intake and eating rate. In addition, 10 mg sibutramine reduced hunger later in the meal whereas 15 mg sibutramine increased fullness early in the meal both actions being consistent with enhanced within-meal satiation. The results provide novel evidence that decreased consumption of a test meal induced by sibutramine is primarily due to reduced eating rate, enhancing the deceleration in cumulative food intake within a meal associated with the development of satiety.^{83,234}

The effects of sibutramine on eating behavior in the UEM provide a template with which to compare novel, appetite-reducing, anti-obesity compounds. Drug-induced changes in food intake and appetite appear to provide a reliable indication of potential weight-reducing efficacy. Therefore, the potential for late stage failure could be reduced by incorporation of a UEM efficacy model in Phase I experimental medicine studies.

Measurement of Anti-Obesity Drug Efficacy and CNS Side-Effects in Experimental Medicine Studies: The Emotional Test Battery Approach

There is considerable evidence that drugs used to treat anxiety and/or depression may have effects on the food intake and body weight of patients.²²¹ Conversely, it is possible that anti-obesity drugs may adversely affect brain reward pathways causing

mood changes such as anhedonia and potentially anxiety and/or depression (e.g., CB1 receptor antagonists, see above). The prevalence of depression and anxiety is high among obese persons seeking treatment and in a recent UK study of 253 patients attending specialist obesity services, 48% had elevated scores for depression and 56% had elevated scores for anxiety on the hospital anxiety and depression (HAD) scale.²²² Therefore, it is valuable to ascertain at an early stage of the drug development process whether a candidate compound/mechanism could cause mood changes and/or exacerbate symptoms of depression or anxiety. For example, it has been reported that CB1 receptor knockout mice demonstrate a depressive state and that CB1 receptor blockade could induce depression.²²³ Although the eligibility criteria reported in the RIO Phase III clinical trials with rimonabant do not mention a specific HAD score at which patients were excluded, the participants in these trials had a mean subscore for depression of approximately three, suggesting that efforts were made to enroll individuals with minimal or no depressive symptoms.¹⁵⁻¹⁷ Consequently, it is uncertain whether the psychiatric safety data of rimonabant presented in the reports of the RIO trials can be generalized to general clinical practice in which a high percentage of obese patients are likely to have a HAD scale subscore for depression that is significantly higher than three.²²⁴ This evidence has been interpreted as suggesting that there is not sufficient evidence from the RIO trials to determine whether rimonabant is safe for use in obese individuals with even mild depression.²²⁴ This conclusion was reinforced by the decision of an FDA Advisory Panel to recommend that the FDA should not approve the drug in the United States, despite the fact that the drug is already on sale in Europe.

Thus in addition to the detection of early biomarkers for obesity it would be valuable if the early clinical development models were sensitive to the potential CNS side effects of anti-obesity compounds. It is also possible that rimonabant (or other compounds in development to treat obesity) could interact with the underlying psychopathology of obese patients who often have reduced self-esteem and other features of depression (see above). Therefore, incorporation of a CNS side-effect battery in UEM studies could be valuable in dose ranging for novel compounds as it may be possible to define a therapeutic window where there are significant effects on food intake but minimal neuropsychiatric adverse effects.

One potential approach would be to incorporate an emotional test battery such as that developed by Harmer and colleagues^{225-227,236} in UEM efficacy studies. Negative biases in thinking, memory, and interpretation of events are believed to be important in maintaining the symptoms of depression and anxiety. Indeed, the main aim of cognitive therapy is to remediate these negative biases in the treatment of these disorders. It has recently been found that antidepressants have similar modulating actions on the neural processing of negative emotional information in healthy volunteers and depressed patients, which may be important in their therapeutic actions. Acute oral or intravenous administration of the SSRI, citalopram (Celexa®), increases the processing of anxiety-related stimuli in healthy volunteers.^{226,232} This mechanism could underlie the known tendency of SSRIs to increase anxiety in patients early in their treatment. Similarly, acute administration of the 5-HT precursor, L-tryptophan in healthy volunteers also increases the recognition of fearful facial expressions²²⁸ while tryptophan depletion, a dietary manipulation that lowers brain 5-HT synthesis, has the opposite

effect.²²⁹ In contrast, chronic administration of citalopram and the selective noradrenaline reuptake inhibitor, reboxetine (Edronax®/Vestra®),²³⁰ decreases the salience of negative emotional stimuli present in facial expressions.²²⁵⁻²²⁷ These results suggest that it is possible to measure bi-directional changes in emotional behavior (that is relevant to anxiety and depression) in healthy volunteers.

Therefore, experimental medicine studies that incorporate a UEM method together with an emotional test battery may prove valuable to determine the efficacy and CNS side-effect profile of anti-obesity drug candidates in Phase I clinical development.

SUMMARY

Obesity is now recognized as a significant predisposing factor to many important chronic diseases, and as a result there is increasing acceptance that medical therapy with drugs to help reduce and maintain body weight may sometimes be appropriate. Currently available treatments have modest efficacy, but concerns over adverse effects and lack of long-term data with regard to clinically relevant outcomes have limited their routine use. Recent and past experience with drugs in this therapeutic area has resulted in regulatory requirements which set a high standard for safety of such drugs. The high prevalence of obesity and perception of significant unmet need has led to increased scientific understanding of the biology of body weight regulation, particularly how this relates to eating behavior. Whilst potential anti-obesity drugs can target many components of energy regulation, the expression of eating behavior in the obese is critical to understanding the etiology of the condition. Drugs which target heightened preference for dietary fat, weakened satiety mechanisms, high disinhibition, and hunger, may be of particular therapeutic benefit. Assessment of the behavioral action of drugs at the preclinical and early clinical stages may be of particular benefit. Many new therapeutic targets have emerged as a result of this new biological understanding, and are proceeding rapidly to clinical development. To avoid previous pitfalls, obesity drug development programs must therefore be especially rigorous in combining the study of efficacy with understanding of potential adverse effects at each stage of development. As with other chronic conditions, it may also be necessary to look at the effects of combinations of treatments, especially as the best long-term outcomes have now been shown for bariatric surgery, which is more efficacious than any currently available drug therapy. Even for those drugs that prove efficacious and safe in the short-term, it will be necessary to conduct long-term studies to determine the effects on outcomes that matter to patients.

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