The Obesity Epidemic: Current and Future Pharmacological Treatments

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Key Words

appetite, satiety, energy balance, adipose tissue, drugs

Abstract

The unabated rise in the prevalence of obesity is a challenge for global health care systems. Efforts to reverse this trend by dietary or behavioral counseling have not been successful, which has stimulated efforts to find a role for pharmacotherapy. Currently only a small number of antiobesity drugs are approved for long-term use and only a few compounds are in clinical development. Despite recent progress in the understanding of the regulation of energy balance, drug discovery has been less productive than expected. In the present review, the clinically available antiobesity agents are discussed. Examples of drug candidates that are currently in development are given and the possible future range of antiobesity agents is illustrated by the targets being addressed in drug discovery. Finally, the efficacy of antiobesity agents and their value in the treatment of obesity are assessed in comparison with other therapeutic approaches, such as surgery and changes in lifestyle.

INTRODUCTION

Obesity has become a significant health problem in industrialized and developing countries. Its prevalence is high, and despite all therapeutic efforts it keeps increasing (1–4). In the adult U.S. population, for instance, the prevalence of overweight in 2004 was estimated to be more than 30%, whereas that of obesity amounted to more than 30%. This means that more than 60% of the adult population exceeded the upper limit of normal BMI (**http://www.cdc.gov/nchs/hus.htm**). Dietary and behavioral treatment of obesity have limited efficacy (5, 6), and pharmacotherapy is not much more successful (7). Although some progress has been made, drug treatment of obesity is still in its infancy and substantial additional efforts are required to improve the efficacy and safety of antiobesity agents.

Prevalence: percentage of a population that is affected by a certain disease at a given point in time

Overweight and obese: a BMI range between 25 and 29.9 kg/m^2 is defined as overweight, a BMI of 30 kg/m^2 and above as obese. At the BMI cut-off point of 30 kg/m^2 the risk of obesity-associated diseases starts to increase exponentially

Body mass index (BMI): the quotient of body weight in kilograms divided by body height in meters squared (BMI = kg/m^2). It correlates with the amount of body fat

Pathophysiology of Obesity

Obesity is the result of a sustained disequilibrium between energy intake and energy expenditure (**Figure 1**). If energy intake is too high or energy expenditure too low, an increase in body weight will develop over time. While in the past the contribution of an increased consumption of high-calorie food has been thought to be the primary factor in the pathogenesis of obesity, reduced physical activity is now thought to be equally or even more important (8, 9). Even a small difference between these parameters becomes relevant if it is maintained over a prolonged period. Conversely, it is generally underestimated how tightly controlled energy balance is under normal circumstances (10). Although on average more than 700,000 kcal are ingested during the course of a year, body weight is usually maintained within a range of ± 1 kg or an equivalent of 7000 kcal, i.e., the long-term regulation of fat stores operates with an accuracy of more than 99%. However, it seems that the defense against weight loss is stronger than against weight gain, which is probably the result of natural selection pressure during evolution when rapid accumulation and efficient maintenance of energy reserves represented a biological advantage (11, 12). Unfortunately the same mechanisms also oppose the efforts to get rid of superfluous pounds (13).

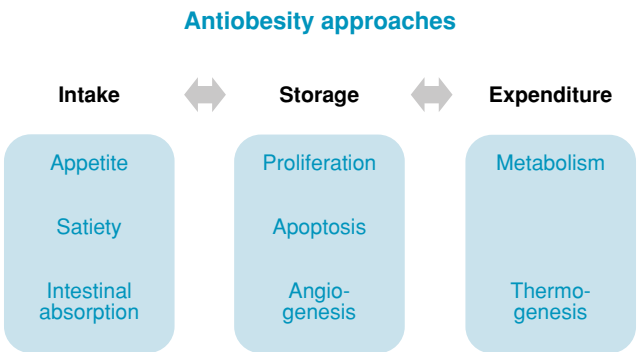

Figure 1

The size of body fat stores is determined by the net balance between energy intake and expenditure over an extended period of time. The most important possible antiobesity approaches are shown.

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

Obesity as a Medical Problem

It is now widely accepted that obesity is more than a cosmetic problem. Several epidemiological studies have documented that excessive fat accumulation is associated with serious diseases and leads to increased morbidity and mortality (14–16). Some of these diseases can be successfully treated, for example, hypertension, type 2 diabetes, and dyslipidemias. It is therefore likely that the increased prevalence of obesity will lead to an increase in morbidity rather than in mortality, thereby causing a substantial rise in health care costs (4, 17). Efficient and safe antiobesity agents would be drugs of first choice and could replace the treatment of the individual diseases associated with obesity by the treatment of obesity itself.

Metabolic syndrome: a cluster of metabolic and cardiovascular risk factors. Insulin resistance is considered to be one of the underlying causes, but a common pathogenetic factor has not yet been identified

It has indeed been demonstrated that even relatively modest decreases in body weight result in significant health benefits. A reduction in body weight of only 5% to 10% leads to a significant fall in blood pressure in patients with hypertension and an improved glycemic control in patients with diabetes (16, 18). However, it remains to be shown whether the effects of such small changes in weight persist in the postobese state when body weight has stabilized or whether they are limited to the dynamic phase of weight loss (19). In any case, the direct correlation between the extent of weight loss and the resulting health benefits makes it desirable that future antiobesity drugs have a higher efficacy than the currently available agents.

If a higher efficacy of antiobesity drugs cannot be achieved, an alternative would be to search for agents that not only reduce fat mass but also act against other therapeutic targets. Such drugs could be used to treat some or all components of the metabolic syndrome (20). However, there are several criteria for the definition of the metabolic syndrome—it may even be diagnosed in patients without obesity—which makes it a difficult indication for the development of antiobesity agents (21, 22).

It is important to recognize that obesity is not only a medical but also a social problem. Patients feel that their body image leads to stigmatization that has serious repercussions on their private and professional lives (23). This is also the reason why quantitative objectives for weight reduction often differ between patients and doctors. While a physician may consider the reduction in risk factors after a moderate weight loss a medical success, a patient may still feel stigmatized because his physical appearance remains far from ideal (24).

Pharmacotherapy of Obesity

The history of drug treatment of obesity is no success story. Dinitrophenol, an uncoupler of mitochondrial oxidative phosphorylation, showed severe toxicity (25) and amphetamine-like agents had addictive properties (26). More recently, two efficient and widely used agents, fenfluramine and dexfenfluramine, had to be withdrawn from the market because of serious adverse events such as cardiac valvular fibrosis and pulmonary hypertension (26, 27). Comparable complications had been encountered earlier with an indirect sympathomimetic agent, aminorex (28).

High standards of efficacy and safety are mandatory for drugs that will be taken not only by obese patients with complications but also by yet symptom-free subjects for

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

Table 1 Antiobesity drugs for long-term use

	Orlistat	Sibutramine	Rimonabant
Organ target	Gut	CNS	CNS/peripheral organs
Molecular target	GI lipases	5HT & NA transporter	CB-1 receptors
Mechanism of action	Enzyme inhibitor	Reuptake inhibitor	Receptor antagonist
Mode of action	Reduced fat uptake	Appetite suppression	Appetite suppression, peripheral actions
Main effect	Reduced caloric intake	Reduced caloric intake	Reduced caloric intake
Additional effects	LDL cholesterol reduction	Increased energy expenditure?	Metabolic effects
Unwanted effects	GI effects	CV effects	CNS effects
Daily dosage	3 × 120 mg	1 × 10 or 15 mg	1 × 20 mg

*For the sake of clarity the information had to be condensed, for details see text.
**Abbreviations: CNS, central nervous system; GI, gastrointestinal; 5HT, 5-hydroxytryptamine = serotonin; NA, noradrenaline; CB-1, cannabinoid type-1; LDL, low-density lipoprotein; CV, cardiovascular.
***From Reference 117, with permission.

the duration of their lives. Antiobesity agents carry also a higher risk for misuse than other drugs, which demands more stringent safety standards in the pharmacotherapy of obesity than in other indications. Moreover, it has to be recognized that tolerability and safety as assessed in carefully controlled trials may not reflect the safety profile of a drug in broad clinical use (29). Owing to the quality standards and exclusion criteria applied in clinical studies, patients in a trial have fewer risk factors and are more intensively monitored than the general patient population. A recent example illustrating this problem is the abrupt increase in hyperkalemia-associated morbidity and mortality in patients treated with the aldosterone antagonist spironolactone. After the publication of positive results in a heart failure trial the prescription rates of this drug steeply increased, and this increase was associated with a higher incidence of lethal hypokalemia (30).

Clinically available antiobesity drugs have been the subject of several recent reviews (31–37). Although in principle there are several approaches to obtain an antiobesity effect, all available drugs and most of those in clinical development act either by appetite suppression or by inhibition of intestinal absorption. Three agents, orlistat (Xenical®), sibutramine (Meridia®, Reductil®), and rimonabant (Acomplia®), were studied in large, randomized, placebo-controlled trials and have been (orlistat, sibutramine) or will soon be (rimonabant) approved for long-term administration. The most prominent features of their pharmacological profiles are summarized in **Table 1** and are discussed in more detail in the following section.

DRUGS ON THE MARKET

Orlistat (Xenical®)

Orlistat is the hydrogenated derivative of lipstatin, a naturally occurring lipase inhibitor of bacterial origin. The drug acts in the lumen of the gut where it blocks the activity of gastrointestinal lipases. Only a minute fraction is absorbed after oral

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

administration, which conveys considerable safety to this drug. By inhibiting the cleavage of ingested triglycerides, orlistat reduces the amount of fatty acids taken up by the intestines in a dose-dependent manner. The mean maximum percentage of ingested fat excreted in the feces was found to be 32% (38). The standard dose of orlistat is 120 mg three times a day (39, 40).

Orlistat has been studied in several double-blind, placebo-controlled trials for periods of up to two years. A meta-analysis of these trials revealed an average reduction in body weight of 2.89 kg (corrected for weight changes in the placebo group) after twelve months of treatment. Most of this loss of body weight occurred during the first six months of treatment. Subsequently, body weight stabilized and remained reduced as long as treatment was continued (7).

This moderate effect on body weight was sufficient to improve several metabolic parameters. A retrospective analysis showed reductions in triglyceride and cholesterol blood levels, improved oral glucose tolerance, and a fall in systolic and diastolic blood pressure. The reduction in LDL cholesterol was more pronounced than would be expected from a reduction in body weight alone, which may be due to the fact that orlistat's mode of action is to reduce the absorption of dietary fat (41). This could also explain the favorable changes in lipid parameters during the early postprandial period in patients treated with orlistat.

The main unwanted effects of orlistat are attributable to its mechanism of action. Nondigested fat remains in the intestinal lumen and causes steatorrhea, flatulence, and fecal incontinence. These adverse effects are enhanced by a high dietary fat intake and may therefore serve as a component of behavioral feedback therapy. Most of these gastrointestinal side effects occur early during treatment and tend to disappear later on (39).

Sibutramine (Meridia®, Reductil®)

Sibutramine is a centrally acting inhibitor of noradrenaline, serotonin, and, to a lesser degree, dopamine reuptake. It acts mainly as an appetite suppressant but may also increase energy expenditure. Chronic treatment with sibutramine results in a reduction in body weight, most of which occurs during the first six months. Further treatment helps to maintain this loss in body weight. According to a meta-analysis of randomized, placebo-controlled trials with doses between 10 and 20 mg per day over 44 to 54 weeks, the average weight loss was 4.45 kg (42), a value not too different from that seen with orlistat.

Several metabolic parameters are improved during sibutramine therapy. In a placebo-controlled one-year trial, small decreases in plasma glucose and glycosylated hemoglobin were observed. Plasma triglycerides were reduced and HDL cholesterol levels slightly increased. In the same trial, systolic and diastolic blood pressure was increased by 4.6 and 2.8 mm Hg, respectively, and heart rate rose by 5.9 beats/min (all results corrected for the corresponding changes in the placebo group) (42). In several trials of shorter duration, i.e., three to six months, blood pressure changes ranged from net reductions to net increases, but a rise in heart rate was consistently observed (43).

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

The cardiovascular effects of sibutramine are probably directly related to its mechanism of action and can be explained as a consequence of its peripheral effects, i.e., an inhibition of noradrenaline reuptake at sympathetic nerve terminals in the arterioles and in the heart. In the central nervous system, the same mechanism of action is known to induce the opposite results. An increase of noradrenaline in the brainstem decreases sympathetic outflow to the periphery via stimulation of alpha-2 receptors, an effect comparable to that achieved with the direct alpha-2 agonists clonidine or alpha-methyl DOPA. The final hemodynamic response to sibutramine is therefore the result of the balance between its peripheral and central effects and depends on the basal sympathetic tone (44). Although it remains to be shown that the central actions of sibutramine are beneficial in patients with an overactivity of the sympathetic nervous system, it is evident that its peripheral cardiovascular actions could at least in part outweigh the beneficial effects of body weight reduction on cardiovascular risk. A large trial, the Sibutramine Cardiovascular Outcome (SCOUT) trial, is underway to clarify these issues (**http://www.clinicaltrials.gov**).

Rimonabant (Acomplia®)

Rimonabant has been launched in the UK and will probably reach the market in several other European countries before the end of 2006. Its approval by the FDA is still pending. Rimonabant belongs to a novel class of antiobesity agents that block the cannabinoid-1 (CB-1) receptor subtype. The appetite-stimulating effects of cannabis—the so-called munchies—have been known for a long time. However, only recent studies with pharmacological blockers of CB-1 receptors have established a role of endocannabinoids in the regulation of appetite (45, 46).

The reduction in body weight observed during treatment with rimonabant is of the same order of magnitude as that seen with the other available agents, orlistat and sibutramine. This has been demonstrated in several double-blind, placebo-controlled trials in which rimonabant was given in addition to a hypocaloric diet at doses of 5 or 20 mg for up to 2 years. In the Rimonabant-in-Obesity (RIO) Europe study, patients with a body mass index (BMI) above 30 kg/m^2 or a BMI greater than 27 kg/m^2, together with treated or untreated dyslipidemia, hypertension, or both, received rimonabant for one year (47). The final weight loss was 1.8 kg in the placebo group and 3.4 and 6.6 kg in the 5 mg and 20 mg rimonabant groups, respectively. The maximum total drug-induced reduction in body weight over placebo amounted to 4.8 kg. Waist circumference, HDL cholesterol, triglycerides, and insulin resistance were also improved with 20 mg of the drug. The most common adverse events were nausea and diarrhea. Mood disorders were more frequent in the rimonabant 20 mg group than in the other groups (47).

In the RIO–North America trial, rimonabant was given at 5 or 20 mg per day over 12 months (48). Compared with the placebo group, a greater reduction in weight (−6.3 versus −1.6 kg) and waist circumference was seen in the 20 mg rimonabant group. Moreover, the fall in plasma triglycerides and the rise in HDL cholesterol were more pronounced in the rimonabant-treated patients. After the end of the first year, rimonabant-treated patients were rerandomized to continued treatment with

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

drug or placebo for another year. At the end of this second year, rimonabant-treated patients had maintained their weight loss and the favorable changes of risk indicators, whereas placebo-treated patients had regained most of their weight. Unfortunately, the interpretation of this trial is limited due to a drop-out rate of almost 50% during the first year, which may have caused a substantial bias in the analysis of the data (49).

In the recently published RIO-Lipids study including overweight or obese patients with dyslipidaemia, the drug was given at doses of 5 or 20 mg per day for 12 months, in addition to a hypocaloric diet (50). At a dose of 20 mg, rimonabant induced a significant weight loss and a reduction in waist circumference. Weight loss occurred during the first nine months of treatment and stabilized thereafter. At the end of the study, weight loss was 2.3 kg in the placebo group, whereas it amounted to 4.2 and 8.6 kg in the groups receiving 5 or 20 mg rimonabant, respectively. Plasma triglycerides were reduced and HDL cholesterol increased. There was no change in the total levels of LDL–cholesterol, but the distribution of LDL particles shifted toward a larger size. Glucose and insulin responses to an oral glucose challenge were reduced, indicating improved glucose tolerance. Adiponectin plasma levels increased significantly, whereas leptin and C-reactive protein were reduced after 20 mg rimonabant. Systolic and diastolic blood pressure was lowered after 20 mg rimonabant, especially in patients with hypertension (50).

Rimonabant showed good tolerability. Overall, discontinuation rates were similar in drug and placebo-treated groups. However, in the 20 mg rimonabant group, more patients discontinued treatment because of adverse effects (depression, anxiety, and nausea) than in the other groups. Side effects in the patients who continued the trial were slightly more frequent in the 20 mg rimonabant than in the placebo group, and consisted mainly of nausea, dizziness, and anxiety (50).

Rimonabant's beneficial effects on risk factors are probably not only attributable to the weight loss induced by its appetite-suppressant effect but also mediated through peripheral effects of the drug. The increase in plasma levels of adiponectin, for instance, could only partially be explained by weight loss alone. In several well-controlled clinical trials, rimonabant has been shown to induce a larger rise in HDL cholesterol than would be expected from the concomitant weight loss. These changes in HDL levels correlated with those of adiponectin and may constitute weight-loss-independent effects of rimonabant. Similarly, the improvement in HbA1c levels was more pronounced than predicted from body weight reduction. These additional actions could be either directly mediated via the blockade of peripheral CB-1 receptors or indirectly via the increased plasma concentrations of adiponectin, an adipokine that has been shown to improve insulin sensitivity (47, 50).

However, the fact that blood pressure was not lowered during rimonabant treatment in the RIO-Europe and RIO–North America trials raises questions (49). In lifestyle weight reduction trials, a weight loss comparable to that observed with 20 mg rimonabant resulted in significant reductions in systolic and diastolic blood pressure (51). Whereas rimonabant appears to induce more beneficial changes in lipid parameters than would be expected from the weight loss alone, such an advantage cannot be claimed for its effects on blood pressure.

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

The fact that more than 13,000 patients have so far been included in clinical trials with rimonabant (6600 in obesity trials and 7000 in smoking cessation trials) seems to provide a solid basis for the safety assessment of this drug. However, it remains to be seen whether the good tolerability record is confirmed when the drug is used in the general obese population. Adverse events on the central nervous system are of main concern, but cardiovascular problems cannot be excluded. CB-1 receptor blockade with rimonabant had detrimental effects in a rat model of myocardial ischemia (52). In three different animal models of hypertension, blockade of CB-1 receptors increased blood pressure, an effect that was absent in normotensive animals (53). A large clinical trial on the effects of rimonabant on the development of coronary atherosclerosis (STRADIVARIUS) has recently been initiated and may clarify at least some of these questions (**http://www.clinicaltrials.gov**).

Other Products

A number of older drugs are still on the market for short-term use in the treatment of obesity, most of them belonging to the class of sympathomimetic agents. Their appetite-suppressing effects tend to diminish after a few weeks and they are therefore only useful as an adjunct treatment during the first few weeks of a weight loss program. Moreover, these drugs have been less intensively studied than the newer antiobesity agents and their adverse effects are not well documented. One of these agents, phenylpropanolamine (PPA), has recently been withdrawn and is no longer available in the United States. Examples of drugs still in use include benzphetamine, diethylpropion, mazindol, phendimetrazine, and phentermine. The pharmacological profile of these and other older or off-label antiobesity agents has recently been reviewed (37, 54).

Numerous over-the-counter products, including homeopathic preparations, are available for weight reduction in various countries. Diverse mechanisms of action are claimed for such products and they are widely used despite inadequate documentation of their safety and efficacy (55, 56).

DRUGS IN CLINICAL DEVELOPMENT

The considerable progress that has been made in the elucidation of the regulation of energy balance (10, 36, 57, 58) is not yet reflected by the pipeline of pharmaceutical companies. Furthermore, despite the remarkable scientific accomplishments in the pathophysiology of obesity, only a few new drugs are currently undergoing clinical trials (59) (**Figure 2**).

The successful development of rimonabant by Sanofi-Aventis has stimulated several competitors to develop their own CB-1 receptor antagonists (e.g., CP-945,598 by Pfizer, **http://www.clinicaltrials.gov**). It is too early to tell whether these compounds will show any advantage over rimonabant. A novel profile may result from a different balance between their central and peripheral effects, and it is conceivable that compounds with an exclusive peripheral action can be designed. However, such agents may suffer from a reduced efficacy as appetite suppressants. Because

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

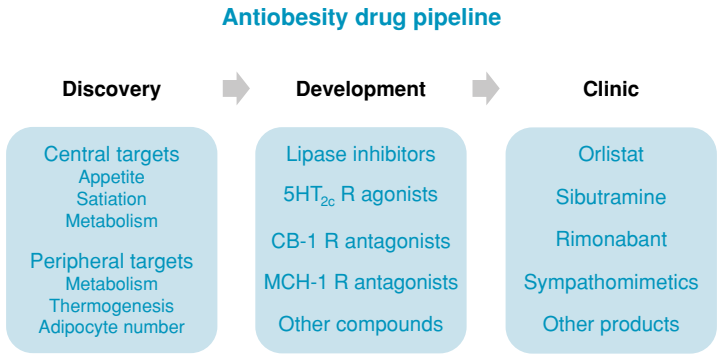

Figure 2

The pipeline of antiobesity drugs is not very impressive. There are two drugs available for long-term use and a third one is close to registration. Some older drugs are still marketed as prescription or over-the-counter medications. The main representatives of candidates in clinical development are follow-ups to existing drugs, e.g., lipase inhibitors, or appetite suppressants with novel mechanisms of action, e.g., agonists of $5HT_{2c}$ or antagonists of melanin-concentrating hormone-1 receptors. Several other compounds are in early stages of clinical development (see text for details). The ever-increasing number of novel molecular targets can be classified into central and peripheral ones. Although most of the antiobesity drugs on the market or in clinical development act on the brain, such agents have the inherent danger of causing central side effects. Drugs acting at peripheral targets may be expected to be safer but it has not yet been convincingly demonstrated that the benefit/risk ratio of peripherally acting drugs is really superior to their centrally acting counterparts. The distinction between central and peripheral targets may prove to be less stringent than previously assumed because interference with central receptors can result in peripheral metabolic effects that are mediated through the autonomic nervous system or other yet unknown pathways. Novel and exclusively peripheral modes of action, such as the modulation of the differentiation, proliferation, or apoptosis of adipocytes, may lead to drugs that directly limit the size of body fat stores.

the average weight loss obtained with rimonabant is not much better than that seen with orlistat or sibutramine, any further reduction in the efficacy of such agents may preclude their successful registration.

A new appetite-suppressing drug in clinical trials is APD 356, a 5-HT_{2c} receptor agonist (**http://www.clinicaltrials.gov**). Such compounds probably have anorexigenic effects comparable to those of 5HT-reuptake inhibitors, but owing to their selectivity for a 5HT receptor subtype should be less prone to induce adverse effects. For the same reason, they should be devoid of the cardiovascular toxicity seen with fenfluramine and dexfenfluramine (27).

Other examples of appetite suppressants with a novel mechanism of action are antagonists of melanin-concentrating hormone (MCH) (60). This peptide is produced by neurons in the lateral hypothalamus and acts as an endogenous appetite-stimulating (orexigenic) agent at the MCH-1 receptor subtype. Consequently, antagonists of the MCH-1 receptors show anorectic activity, and several representatives of this class are in preclinical or early clinical development (e.g., GW 856464 in Phase I, **http://www.gsk.com**).

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

Drugs that reduce gastric emptying may enhance satiation. Such a mechanism is probably a component of the appetite-suppressing action of antidiabetic agents such as pramlintide, an analog of amylin that has been developed for the indication of type 2 diabetes (61, 62). Appetite suppression would be an interesting addition to its clinical profile and could be the basis for its registration as an antiobesity drug (AC137 in Phase II, Amylin, **http://www.amylin.com**).

Inhibitors of gastrointestinal lipases probably have a maximum efficacy that cannot be surpassed. However, a reduced frequency of adverse effects could be a clinical advantage. It appears that ATL-962 (cetilistat), a possible successor to orlistat, may offer a better tolerability (Phase III at Alizyme, **http://www.alizyme.co.uk**).

DRUG DISCOVERY

Central Targets/Hypothalamic Mediators

Over the past decade, knowledge about the central regulation of energy balance has enormously increased (10, 36, 58). By the identification of leptin as the first peptide hormone that is expressed in adipose tissue and informs the brain about the status of the energy reserves of the organism, a new concept for the regulation of body fat mass has been established (63). Subsequently, this pathway has been extensively studied (64) and it is now well established that leptin is expressed in adipose tissue and released into the blood. Its circulating levels are related to the number and size of adipocytes (**Figure 3**).

Circulating leptin reaches the hypothalamus where it acts via specific leptin receptors on two distinct neuronal populations in the arcuate nucleus. Activation of leptin receptors stimulates neurons expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (CART) while it inhibits neurons expressing neuropeptide Y (NPY) and Agouti-related protein (AgRP). POMC is the precursor of alpha-melanocyte-stimulating hormone (α-MSH), which activates the melanocortin-4 (MC-4) receptor subtype in the paraventricular nucleus to reduce appetite. CART is another anorexigenic mediator. Conversely, NPY stimulates appetite by acting on NPY-1 or NPY-5 receptors, whereas AgRP produces the same effect by acting as an inverse agonist of MC-3 and MC-4 receptors. The stimulation of NPY- and AgRP-containing neurons has therefore a twofold effect: it increases appetite not only by activation of orexigenic NPY receptors but also by blockade of anorexigenic MC-4 receptors (10, 58).

Leptin. Despite the well-established importance of these hypothalamic pathways, no agonists of leptin receptors are currently in clinical development. Leptin itself showed disappointing results in obese patients (65), which can be explained by the occurrence of leptin resistance in a high proportion of these patients. However, for a next generation of drugs the mechanisms involved in the development of leptin resistance could become new targets (66).

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

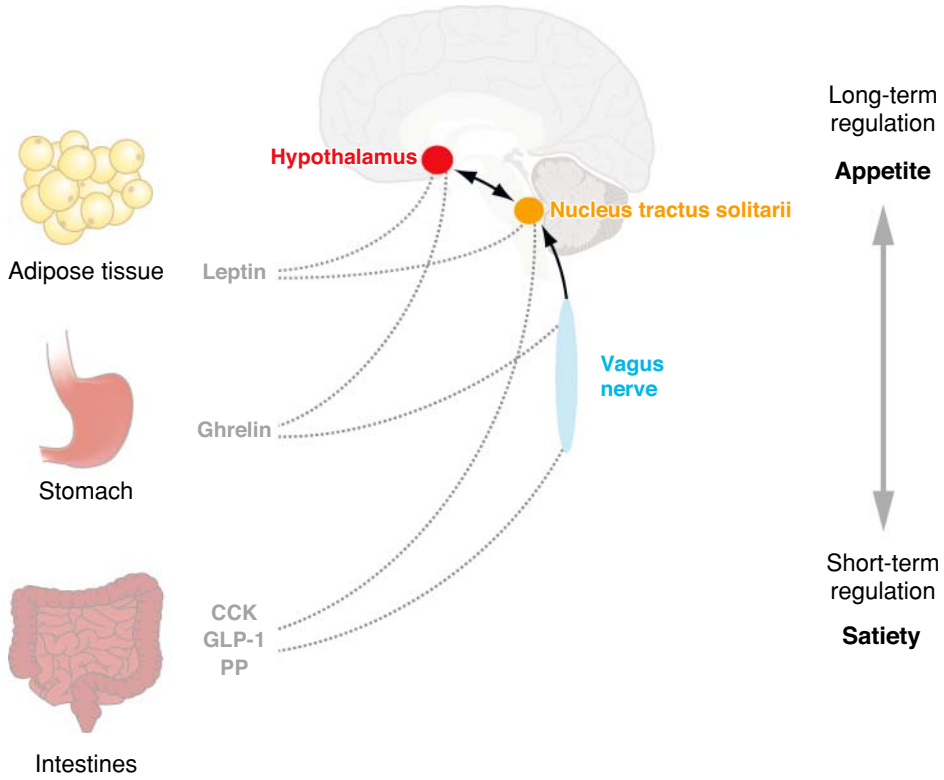

Figure 3

Peripheral signals influence appetite or satiation by a direct action on certain brain areas, by indirect effects via the vagus nerve, or both. Such signals originate in the adipose tissue (adiposity signals) or the gastrointestinal tract (satiety signals). While adiposity signals such as leptin are mainly responsible for the long-term regulation of energy balance, the signals from the gastrointestinal tract are involved in the short-term regulation of satiety. At the level of the hypothalamus all these different mechanisms are integrated and modulate each other's sensitivity and efficacy. The most important adiposity signal is leptin, which acts on specific receptors in the hypothalamus and the hindbrain. In the hypothalamus, the activation of leptin receptors leads to the stimulation of neurons containing pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript and to the inhibition of neurons producing neuropeptide Y (NPY) and Agouti-related protein. The downstream pathways include the activation of hypothalamic melanocortin-4 receptors, which finally lead to appetite suppression. Among the gastrointestinal hormones, ghrelin, which is mainly derived from the stomach, is the only peptide that stimulates appetite. It acts directly on NPY neurons in the hypothalamus but also via vagal afferents. Several intestinal peptides are known to increase satiation during and after a meal. Cholecystokinin (CCK) and pancreatic polypeptide (PP) act on the hindbrain directly and through vagal afferents. Peptide YY and oxyntomodulin (not shown) are thought to influence mainly the hypothalamus. Glucagon-like peptide 1 (GLP-1) has antidiabetic actions but also an appetite-reducing effect.

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

Neuropeptide Y. After leptin turned out to be not suitable for the treatment of the most common forms of obesity, the pathways downstream of leptin, e.g., NPY and the melanocortins, became a focus of drug discovery. However, the interest in NPY antagonists vanished after several studies in knockout mice showed that neither the elimination of NPY nor that of its most important receptor subtypes, NPY Y1 or NPY Y5, resulted in a lean phenotype (67, 68). These observations made it unlikely that NPY antagonists would be an efficient therapeutic approach to obesity.

Melanocortins. By contrast, numerous experimental and clinical findings strongly suggest an important role of the melanocortin system in the regulation of food intake and energy expenditure. In genetically modified mice, any interruption of this pathway, be that by eliminating the endogenous agonist α-MSH, by overexpressing its endogenous antagonist AgRP, or by knocking out the MC-4 receptor, resulted in obesity (69). This concept was corroborated by the finding that mutations of the MC-4 receptor in humans constitute the most frequent monogenic form of obesity, accountable for up to 5% of all cases with severe obesity (70).

For this reason, priorities in drug discovery have shifted to the melanocortin system, but the development of MC-4 receptor agonists has proceeded less successfully than expected. One obstacle appears to be the fact that hypothalamic MC-4 receptors mediate not only a reduction in food intake but also an increase in blood pressure and heart rate (71, 72) and penile erection (73). These effects cannot be dissociated from that on appetite. Consequently, a melanocortin receptor agonist with unclassified receptor subtype selectivity, PT-141 (Palatin), is currently being developed for the indication of sexual dysfunction rather than for obesity (74). In recent studies, it has been shown that signaling pathways appear to diverge downstream of the MC-4 receptor (75). Interaction with more distal targets could therefore make it possible to achieve selective pharmacological effects.

Central Targets/Gut Hormones

While the long-term regulation of energy stores appears to mainly depend on signals from adipose tissue, its short-term regulation is mediated by neural and hormonal input from the gastrointestinal system (57, 76). Several appetite-suppressing, anorexigenic peptides, such as cholecystokinin or peptide YY, are complemented by ghrelin, an appetite-stimulating, orexigenic agent derived from the stomach. Glucagon-like peptide 1 (GLP-1) has antidiabetic actions but also an appetite-reducing effect (77). The most important elements involved in the central regulation of food intake and their pathways are shown in **Figure 3**.

Peptide YY. After the failure of cholecystokinin analogs as appetite-lowering drugs, other gastrointestinal hormones have gained renewed interest, the most recent example being PYY3–36 (78). This peptide is the main circulating form of PYY, which is produced in the large intestine and is released in response to a meal. Although its anorexigenic effects in rodents are a matter of controversy (79), its effects in humans appeared to be robust enough to warrant its development as an antiobesity drug

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

(80). Owing to its peptidic nature, this hormone cannot be orally administered. Currently, its suitability for intranasal delivery is being investigated (Phase II at Nastech, **http://www.nastech.com**), but doubts remain as to whether it will have sufficient appetite-lowering efficacy in patients.

Ghrelin. The only gut hormone identified to date that stimulates appetite is ghrelin, a peptide that was originally described as a growth hormone secretagogue (81, 82). Ghrelin is mainly produced in the stomach, secreted into the blood, and reaches growth hormone secretagogue receptors in the hypothalamus. Circulating levels of ghrelin increase before a meal and start to decrease immediately thereafter. Antagonists or inverse agonists of ghrelin receptors could therefore be novel anorexigenic agents that reduce the frequency of meals. However, such compounds will only be effective if ghrelin significantly contributes to the stimulation of appetite before a meal (83) (**Figure 3**).

Peripheral Targets/Energy Expenditure

Research on energy expenditure has proven to be the least productive approach to the identification of novel drug targets. Much attention has been devoted over the past decades to the stimulation of β-3 adrenergic receptors (84). The stimulation of these adipose-specific adrenergic receptors should lead to an increased expression of uncoupling protein 1 (UCP1), thereby increasing thermogenesis. The first generation of β-3 agonists was selected based on preclinical studies in rodents, but failed in clinical development apparently due to lack of potency at the human receptor. The next generation of compounds was tailored to the human receptor but still did not provide convincing results. A general problem of this approach in patients is probably the lack of a physiological substrate. Mitochondria-rich brown adipose tissue, which expresses UCP1, is important for temperature regulation in rodents and hibernating animals but disappears in human infants after birth. It has been hypothesized that brown fat cells may reappear during chronic treatment with β-3 adrenergic agonists (85). Further studies with the compounds still remaining in development [e.g., N-5984 by Kyorin (86); solabegron by GlaxoSmithKline, **http://www.gsk.com**; both in Phase I for diabetes] may help to clarify this point.

Several years ago, two novel putative uncoupling proteins, UCP2 and UCP3, were identified (87). Particularly the latter, which is located in skeletal muscle, was thought to be responsible for heat production in this tissue and therefore represents an interesting pharmacological target. However, neither of these two molecules appears to serve as a thermogenic protein in the strict sense. Whereas UCP2 probably plays a role in the regulation of insulin secretion from pancreatic β-cells, the physiological function of UCP3 is still uncertain (88, 89).

Peripheral Targets/Metabolism

In recent years, it has been convincingly demonstrated that body fat is not an inactive energy deposit but expresses a variety of important mediators with autocrine,

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

paracrine, or endocrine function (90–92). These substances, called adipocytokines or adipokines, show a broad spectrum of effects and some important examples are illustrated in **Figure 4**.

In the recent past, remarkable progress has been made in elucidating autocrine, paracrine, and endocrine functions of adipose tissue through the identification of numerous so-called adipokines that are produced and released in relation to the number and size of adipocytes (90–92). One of the most important representatives

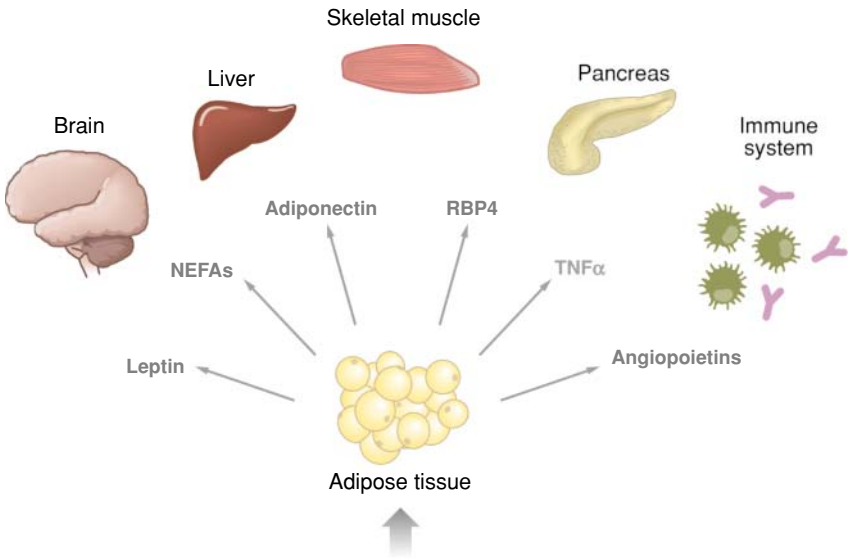

Figure 4

Adipose tissue is not an inert storage compartment, but it acts as an endocrine organ. In addition to metabolic products such as nonesterified fatty acids (NEFAs), several other factors are released. These adipocytokines or adipokines act at various sites and have endocrine, paracrine, or autocrine function. Leptin's main role is to inform the brain about the status of the body's energy reserves, but it also has other important actions, e.g., on the immune system. Adiponectin appears to play a role in the regulation of insulin sensitivity and could thereby influence diverse metabolic functions. Serum retinol-binding protein-4 (RBP4) appears to be linked with insulin resistance. Tumor necrosis factor α (TNFα) is an example of a cytokine that shows important systemic activity in rodents and has been shown to cause insulin resistance in several obesity models. In humans it seems to act mainly as an autocrine factor because it is not released from adipose tissue. Angiopoietins are adipokines involved in the regulation of angiogenesis. Whether such factors are not only responsible for the vascularisation of adipose tissue but also contribute to the increased risk of metastatic disease in obesity is not yet clear. Under physiological conditions the expression of adipokines is under the control of hormonal and neural inputs. In recent years, it has become evident that adipokines also mediate the effect of drugs. Thiazolidinediones appear to act, at least in part, through the release of adiponectin. The possible contribution of adiponectin to the peripheral actions of rimonabant is discussed in more detail in the text.

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

of this class of endogenous mediators is adiponectin, whose secretion is negatively correlated with the amount of adipose tissue (93). The relative lack of adiponectin in obese subjects appears to be one of the main factors causally related to insulin resistance in liver and muscle. Conversely, an increased production of adiponectin induced by thiazolidinediones could be one of the main mechanisms of action of these important antidiabetic drugs (94). As discussed above, the stimulation of adiponectin production could be one of the most important peripheral actions of rimonabant (**Figure 4**). However, not all adipokines that have been shown to be active in rodents are also active in humans. Such species differences have been demonstrated for TNFα and resistin (95).

There are other ways to improve insulin sensitivity. One of the most promising targets is PTP-1B, a protein tyrosine phosphatase that is important for insulin and leptin signaling. Inhibition of PTP-1B expression in mice has been shown to improve insulin sensitivity and decrease body weight in genetically and dietary obese mouse strains. However, protein tyrosine phosphatases represent a novel class of drug targets, which have inherent risks. Their intracellular location and their diverse functions in various pathways are a challenge for the design of specific agents with suitable pharmacodynamic and pharmacokinetic properties (92).

Peripheral Targets/Fat Storage

Several enzymes involved in lipogenesis or lipolysis could serve as targets for drugs that regulate the size of lipid stores. Stearoyl-CoA-desaturase 1 (SCD1) is responsible for a critical step in triglyceride synthesis (96). Although homozygous KO mice showed abnormalities of skin and hair, heterozygous KO mice showed no such undesirable complications. This suggests that partial inhibition of SCD1 could be a feasible antiobesity approach. Likewise, partial inhibition of acyl-CoA:diacylglycerol-acyltransferase-1 (DGAT-1), a microsomal enzyme that catalyses the final step in triglyceride synthesis, seems to be sufficient to provide resistance to diet-induced obesity in mice (97). Acylation-stimulating protein increases triglyceride synthesis by activating DGAT, but its inhibition may have complex effects on lipid metabolism, which could increase the risk for atherosclerosis (92). AOD 9604 (Phase II at Metabolic Pharmaceuticals, **http://www.metabolic.com.au**) is a human growth hormone fragment that has a selective effect on adipose tissue where it promotes fat oxidation. It is devoid of the diabetogenic and the possible tumorigenic effects of growth hormone (98), which precluded the use of full-length growth hormone as an antiobesity agent.

The number of adipocytes could be directly reduced either by inhibition of adipocyte differentiation and proliferation or by activation of adipocyte apoptosis. The growth of adipose tissue could be indirectly affected by limiting blood supply with antiangiogenic drugs (99). Although these approaches are in principle possible, their practical application in pharmacotherapy is fraught with considerable problems. Tissue selectivity is one obstacle, whereas the metabolic consequences of a decreased capacity for lipid storage in adipocytes, i.e., lipid accumulation in skeletal muscle and liver, are another issue. It is known that lack of adipose tissue leads to lipotoxicity in patients suffering from inherited or drug-induced lipodystrophy (100). However,

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

experimental findings in mice suggest that ablation of adipose tissue may result in an enhanced metabolic rate and thereby prevent increased deposition of lipids in nonadipose tissues (99).

PERSPECTIVES AND OUTLOOK

Efficacy of Antiobesity Agents

The limited efficacy of all currently available drugs becomes particularly obvious when the results of pharmacotherapy are compared with those of bariatric surgery (37) (see Mimicking Caloric Restriction sidebar). Even with the least invasive procedure, gastric banding, more pronounced body weight reductions can be achieved than with drug treatment. The most widely used bypass technique, the roux-en-Y ileo-jejunal anastomosis with reduction of the gastric fundus, results in an even more pronounced weight loss. A meta-analysis showed that surgical treatment of severely obese patients resulted in a 20 to 30 kg weight loss that was maintained for 10 years or longer (101). However, the strong weight reduction after surgical interventions may have a cost. A recent study revealed a high rate of rehospitalizations reflecting postoperative complications (102).

It is conceivable that pharmacotherapy could eventually benefit from what may be learned from surgery. It has been speculated that the high efficacy of gastric banding or gastrointestinal bypass surgery is not only the result of the anatomical changes but also

MIMICKING CALORIC RESTRICTION

It is well established that caloric restriction (CR) triggers an adaptive drop in metabolic rate in rodents, nonhuman primates, and humans (118–121). This adaptation plays a key role in the body weight rebound after weight loss observed in most patients. However, CR also instigates beneficial effects, namely a lower incidence of metabolic disorders associated with aging, such as overweight or obesity, insulin resistance, and cardiovascular disease. CR has been shown to increase lifespan in organisms ranging from yeast to rodents, and is probably also effective in nonhuman primates (122–124). The detailed mechanisms responsible for these stress-adaptive responses are not yet fully understood. Low plasma levels of insulin or low activity of the insulin signaling pathway have been associated with longer lifespan in animals (123), and recently a family of proteins known as SIRTs, or Sirtuins, has been implicated in the effect of CR on lifespan extension and possibly on the prevention of metabolic disorders (125, 126). It might thus be possible to recapitulate the beneficial effects of CR with drugs. Such caloric restriction mimetics would target the same metabolic and stress-response pathways without actually decreasing calorie intake, and if successful, come close to a magic bullet against obesity and aging (122).

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

related to persistent adaptations in the production of gastrointestinal hormones (103). If these endocrine modifications were mimicked by pharmacological means, agents with improved efficacy could be expected. However, it may be necessary to affect more than one of several gastrointestinal mediators to reach this goal. Whether this can be achieved by a single drug or requires drug combinations is an open question.

Counterregulation

Because energy homeostasis is the result of a finely tuned balance between energy intake and expenditure, any pharmacological interference invariably leads to compensatory changes in either parameter (104). It is noteworthy that all currently available drugs and most of the drug candidates in clinical development are directed toward a reduction in energy intake. The amount of weight loss achievable with such agents is probably limited by the same counterregulatory mechanisms that are activated during starvation and may also be responsible for the usual failure of dietary approaches to obesity (13). By trying to reestablish the initial weight that is sensed as a set point, these counterregulatory mechanisms impose an upper limit on the amount of weight loss achievable with pharmacotherapy.

Such a limitation could be avoided if a drug not only induced a transient functional response but also induced persisting structural changes. Experimental and clinical results with Axokine, a derivative of ciliary neurotrophic factor that acts as a strong appetite suppressant, suggest that this might be feasible (105, 106). After the end of treatment with Axokine, body weight remained reduced as if a change in the set point of body weight regulation had occurred. Recent experimental studies may provide an explanation for this phenomenon. When Axokine was infused into the brain of mice for several days, it was found that the subsequent long-lasting reduction in food intake and body weight was associated with an increased number of neurons (107). These observations could provide a new concept in the search for novel antiobesity drugs that would take advantage of synaptic plasticity (108) as a means to enhance the long-term efficacy of drug treatment.

Systems Biology

The concept to design drugs that selectively reduce body fat mass without affecting other body functions is difficult to put into practice. The regulation of body weight is tightly linked to many other neural and endocrine regulatory cycles. This points to one of the most important issues in the search for novel antiobesity drug targets, namely, the need for an integrative, or systems biology, approach. Only by a quantitative analysis of the contribution of each individual component to the overall regulation of energy balance can a hierarchy of mechanisms and mediators be established (109). This would make it possible to distinguish between strong and weak, i.e., more or less important, mechanisms. Furthermore, all interactions also need to be analyzed over time to distinguish between short- and long-acting systems. Such studies have previously been performed in cardiovascular physiology (110) and have helped to clarify the priorities of mechanisms contributing to the regulation of blood pressure

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

(111) and cardiac function (112). Such an approach would help to select the most promising targets for drug discovery from the ever increasing number of mechanisms and mediators involved in the regulation of energy balance. This still may not be enough to adequately address the clinical situation. In humans, the components of energy metabolism, such as food intake or physical activity, are complex behavioural functions that are strongly influenced by social and environmental factors.

Place of Drugs in the Treatment of Obesity

When drug treatment is used in combination with lifestyle changes, the results of both approaches are additive. This has been confirmed again in a recent trial in

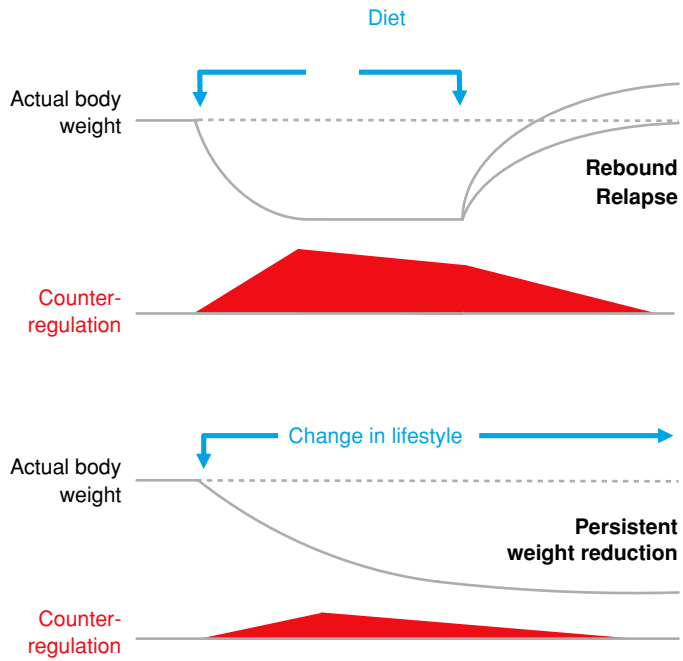

Figure 5

One of the main unresolved problems in antiobesity therapy is the activation of strong counterregulatory mechanisms. These systems are stimulated by any attempt to lose weight regardless of whether starting from a normal or an increased level. The counterregulatory adaptive responses mainly consist of a drop in metabolic rate and usually persist until body fat stores have been restored. This is one of the reasons why temporary periods of dieting only lead to a transient weight loss. After the phase of reduced caloric intake is terminated, body weight increases toward the initial level (relapse) or beyond (rebound). The only promising way to achieve a persistent reduction in body weight is a change in lifestyle, which includes not only nutritional measures but also physical exercise. All these efforts must not be exaggerated but should rather become a part of daily life. In that way, the initial counterregulatory responses can be kept at a minimum and will eventually disappear when the organism has slowly but progressively adopted a new set point for the maintenance of body weight.

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

which continuous lifestyle modification counseling was combined with sibutramine over a period of one year (113). Frequent recording of food intake in the latter group resulted in additional weight loss. In contrast, when lifestyle modification counseling was only provided at the beginning of therapy it did not have such an effect. This trial strengthens the previous experience with combinations of drug treatment and behavioral therapy and strongly supports the notion that a chronic disease such as obesity needs long-term treatment. Whenever temporary measures are applied, a phase of weight loss will be followed by weight regain or by an overshooting weight increase (**Figure 5**).

Even if more efficacious antiobesity drugs eventually become available, the chronic treatment of a substantial part of the population with drugs cannot be the only approach to the obesity epidemic. In light of the limited success of antiobesity therapy, it is obvious that the prevention of overweight and obesity, especially in children and adolescents, is of particular importance. Various programs at the societal, school, and family levels have been designed and implemented (114, 115). In all attempts to lower body weight, it needs to be emphasized that the basis of antiobesity treatment is not a transient period of restrictive diet, intensive exercise, or drug treatment but a sustainable change in lifestyle (116) (**Figure 5**).

SUMMARY POINTS

1. The worldwide prevalence of obesity is rising at an alarming rate. In particular, the increasing number of overweight or obese children and adolescents is a matter of concern.
2. Obesity is not only a cosmetic or social problem but is associated with serious diseases such as type 2 diabetes, dyslipidemia, hypertension, and malignancies.
3. Because dietary and behavioural treatment of obesity usually provide only limited benefit, there is a need for efficient and safe drugs.
4. Despite intensive efforts in academia and industry, only two drugs (orlistat and sibutramine) are currently available for long-term treatment. A third one, rimonabant, started to reach its first markets during the course of 2006.
5. The elucidation of novel mediators and mechanisms in the regulation of energy balance has made remarkable progress in recent years. However, drug discovery has been less successful than expected and the pipeline of antiobesity drug candidates is not impressive.
6. Most efforts in pharmaceutical research have been devoted to drugs that reduce energy intake either by suppressing appetite or by limiting the intestinal absorption of lipids. Stimulation of energy expenditure has so far not provided novel antiobesity agents. Attempts to reduce the size of energy stores by directly targeting adipose tissue are in an early exploratory phase.

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

7. Any short-term treatment of obesity is prone to result only in a temporary weight loss owing to the activation of counterregulatory responses that have been shaped during evolution.
8. Currently, the only way to achieve a long-lasting weight reduction is through a change in lifestyle, including nutritional measures and physical activity. Future drugs should not only help to initiate but also to maintain such a long-term reduction in body weight. In the majority of cases, this may require life-long treatment.

UNRESOLVED ISSUES/FUTURE DIRECTIONS

1. Ideal profile of an antiobesity drug. The main objective of the pharmacotherapy of obesity is to achieve a reduction in body weight by the selective loss of body fat mass. An ideal antiobesity drug should lower body weight more than a low-calorie diet and should not induce counterregulatory mechanisms that may limit its efficacy. It should be possible to combine such a drug with other pharmacological agents, diet, and physical exercise. Moreover, such a drug should be well tolerated and be devoid of long-term toxicity, and, in particular, should not aggravate diseases associated with obesity. Its pharmacokinetic properties should make it suitable for a once-daily oral administration to ensure patient compliance.
2. Unrealistic expectations concerning antiobesity drugs. A frequently encountered misconception in the treatment of obesity is the assumption that a drug has lost its efficacy when body weight is stabilizing at a lower level during treatment. In pharmacological terms, this means that a new steady state has been achieved and the drug effects are counterbalanced by compensatory mechanisms. This becomes evident when treatment is terminated and body weight rises again toward the initial values. Although such phenomena are generally accepted for established drugs in other chronic indications, antiobesity agents still meet unjustified criticism because it is expected that body weight should continue to fall during chronic treatment and remain reduced after drug treatment has been stopped.
3. Life-long pharmacotherapy. While life-long drug treatment of many chronic diseases is fully accepted by the general public and the medical community, the long-term pharmacotherapy of obesity is still a matter of debate. There is a wide-spread belief that obesity can be prevented or reversed by simple measures that are solely based on the patients' willful decision, i.e., their adherence to dietary and behavioral advice. However, the experience with weight loss regimens suggests that in most cases, continuous drug treatment is necessary to maintain a drug-induced weight loss.

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

4. Pharmacoprevention. If a clear benefit of drug treatment for obese patients can be shown by a convincing reduction in hard endpoints, the pharmacotherapy of obesity may not only become equally accepted as that of other chronic diseases but may even reduce the use of antihypertensive or antidiabetes medications. Because a huge number of patients would then be exposed to antiobesity drugs, their tolerability and safety must be at least as good as that of the modern antihypertensive agents, which imposes a very high standard.

DISCLOSURE STATEMENT

O. Boss is an employee of Sirtris Pharmaceuticals, Inc., a company involved in drug development against metabolic diseases (mostly diabetes).

LITERATURE CITED

1. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. 2004. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA* 291:2847–50
2. Haslam DW, James WP. 2005. Obesity. *Lancet* 366:1197–209
3. Prentice AM. 2006. The emerging epidemic of obesity in developing countries. *Int. J. Epidemiol.* 35:93–99
4. Yach D, Stuckler D, Brownell KD. 2006. Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. *Nat. Med.* 12:62–66
5. Katz DL. 2005. Competing dietary claims for weight loss: finding the forest through truculent trees. *Annu. Rev. Public Health* 26:61–88
6. Tsai AG, Wadden TA. 2005. Systematic review: an evaluation of major commercial weight loss programs in the United States. *Ann. Intern. Med.* 142:56–66
7. Li Z, Maglione M, Tu W, Mojica W, Arterburn D, et al. 2005. Meta-analysis: pharmacologic treatment of obesity. *Ann. Intern. Med.* 142:532–46
8. Hill JO, Wyatt HR. 2005. Role of physical activity in preventing and treating obesity. *J. Appl. Physiol.* 99:765–70
9. Bensimhon DR, Kraus WE, Donahue MP. 2006. Obesity and physical activity: a review. *Am. Heart J.* 151:598–603
10. Friedman JM. 2004. Modern science versus the stigma of obesity. *Nat. Med.* 10:563–69
11. Chakravarthy MV, Booth FW. 2004. Eating, exercise, and "thrifty" genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases. *J. Appl. Physiol.* 96:3–10
12. Schwartz MW, Niswender KD. 2004. Adiposity signaling and biological defense against weight gain: absence of protection or central hormone resistance? *J. Clin. Endocrinol. Metab.* 89:5889–97

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

13. Hofbauer KG, Huppertz C. 2002. Pharmacotherapy and evolution. *Trends Ecol. Evol.* 17:328–34
14. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. 2003. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N. Engl. J. Med.* 348:1625–38
15. Lazar MA. 2005. How obesity causes diabetes: not a tall tale. *Science* 307:373–75
16. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, et al. 2006. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Circulation* 113:898–918
17. Flegal KM. 2005. Epidemiologic aspects of overweight and obesity in the United States. *Physiol. Behav.* 86:599–602
18. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, et al. 2002. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* 346:393–403
19. Aucott L, Poobalan A, Smith WC, Avenell A, Jung R, Broom J. 2005. Effects of weight loss in overweight/obese individuals and long-term hypertension outcomes: a systematic review. *Hypertension* 45:1035–41
20. Moller DE, Kaufman KD. 2005. Metabolic syndrome: a clinical and molecular perspective. *Annu. Rev. Med.* 56:45–62
21. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, et al. 2005. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 112:2735–52
22. Kahn R, Buse J, Ferrannini E, Stern M. 2005. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 28:2289–304
23. Puhl RM, Brownell KD. 2003. Psychosocial origins of obesity stigma: toward changing a powerful and pervasive bias. *Obes. Rev.* 4:213–27
24. Dalle Grave R, Calugi S, Magri F, Cuzzolaro M, Dall' Aglio E, et al. 2004. Weight loss expectations in obese patients seeking treatment at medical centers. *Obes. Res.* 12:2005–12
25. Harper JA, Dickinson K, Brand MD. 2001. Mitochondrial uncoupling as a target for drug development for the treatment of obesity. *Obes. Rev.* 2:255–65
26. Kolanowski J. 1999. A risk-benefit assessment of antiobesity drugs. *Drug Saf.* 20:119–31
27. Yanovski SZ, Yanovski JA. 2002. Obesity. *N. Engl. J. Med.* 346:591–602
28. Fishman AP. 1999. Aminorex to fen/phen: an epidemic foretold. *Circulation* 99:156–61
29. Patel MR, Donahue M., Wilson PW, Califf RM. 2006. Clinical trial issues in weight-loss therapy. *Am. Heart J.* 151:633–42
30. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, et al. 2004. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. *N. Engl. J. Med.* 351:543–51
31. Chiesi M, Huppertz C, Hofbauer KG. 2001. Pharmacotherapy of obesity: targets and perspectives. *Trends Pharmacol. Sci.* 22:247–54

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

32. Halford JC. 2004. Clinical pharmacotherapy for obesity: current drugs and those in advanced development. *Curr. Drug Targets* 5:637–46
33. Bays HE. 2004. Current and investigational antiobesity agents and obesity therapeutic treatment targets. *Obes. Res*. 12:1197–211
34. Nisoli E, Carruba MO. 2004. Emerging aspects of pharmacotherapy for obesity and metabolic syndrome. *Pharmacol. Res*. 50:453–69
35. Korner J, Aronne LJ. 2004. Pharmacological approaches to weight reduction: therapeutic targets. *J. Clin. Endocrinol. Metab*. 89:2616–21
36. Flier JS. 2004. Obesity wars: molecular progress confronts an expanding epidemic. *Cell* 116:337–50
37. DeWald T, Khaodhiar L, Donahue MP, Blackburn G. 2006. Pharmacological and surgical treatments for obesity. *Am. Heart J*. 151:604–24
38. Zhi J, Melia AT, Guerciolini R, Chung J, Kinberg J, et al. 1994. Retrospective population-based analysis of the dose-response (fecal fat excretion) relationship of orlistat in normal and obese volunteers. *Clin. Pharmacol. Ther.* 56:82–85
39. Hauner H. 2004. Orlistat. See Ref. 127, pp. 219–43
40. Curran MP, Scott LJ. 2004. Orlistat: a review of its use in the management of patients with obesity. *Drugs* 64:2845–64
41. Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, et al. 1999. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* 281:235–42
42. Arterburn DE, Crane PK, Veenstra DL. 2004. The efficacy and safety of sibutramine for weight loss: a systematic review. *Arch. Intern. Med*. 164:994–1003
43. Ryan DH. 2004. Sibutramine. See Ref. 127, pp. 245–66
44. Birkenfeld AL, Schroeder C, Pischon T, Tank J, Luft FC, et al. 2005. Paradoxical effect of sibutramine on autonomic cardiovascular regulation in obese hypertensive patients—sibutramine and blood pressure. *Clin. Auton. Res.* 15:200–6
45. Di Marzo V, Matias I. 2005. Endocannabinoid control of food intake and energy balance. *Nat. Neurosc*. 8:585–89
46. Pertwee RG. 2006. Cannabinoid pharmacology: the first 66 years. *Br. J. Pharmacol*. 147:S163–71
47. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. 2005. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 365:1389–97
48. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. 2006. RIO-North America Study Group. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 295:761–75
49. Simons-Morton DG, Obarzanek E, Cutler JA. 2006. Obesity research—limitations of methods, measurements, and medications. *JAMA* 295:761–75
50. Després JP, Golay A, Sjostrom L. 2005. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N. Engl. J. Med*. 353:2121–34

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

51. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. 2003. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* 42:878–84
52. Wagner JA, Hu K, Bauersachs J, Karcher J, Wiesler M, et al. 2001. Endogenous cannabinoids mediate hypotension after experimental myocardial infarction. *J. Am. Coll. Cardiol.* 38:2048–54
53. Batkai S, Pacher P, Osei-Hyiaman D, Radaeva S, Liu J, et al. 2004. Endocannabinoids acting at cannabinoid-1 receptors regulate cardiovascular function in hypertension. *Circulation* 110:1996–2002
54. Moyers SB. 2005. Medications as adjunct therapy for weight loss: approved and off-label agents in use. *J. Am. Diet. Assoc*. 105:948–59
55. Dulloo AG. 2004. Dietary supplements and herbal preparations. See Ref. 127, pp. 405–19
56. Greenway FL, Heber D. 2004. Herbal and alternative approaches to obesity. In *Handbook of Obesity*, ed. GA Bray, C Bouchard, pp. 329–58. New York: Marcel Dekker
57. Badman MK, Flier JS. 2005. The gut and energy balance: visceral allies in the obesity wars. *Science* 307:1909–14
58. Schwartz MW, Porte DJ. 2005. Diabetes, obesity, and the brain. *Science* 307:375–79
59. Gura T. 2003. Obesity drug pipeline not so fat. *Science* 299:849–52
60. Mashiko S, Ishihara A, Gomori A, Moriya R, Ito M, et al. 2005. Antiobesity effect of a melanin-concentrating hormone 1 receptor antagonist in diet-induced obese mice. *Endocrinology* 146:3080–86
61. Schmitz O, Brock B, Rungby J. 2004. Amylin agonists: a novel approach in the treatment of diabetes. *Diabetes* 53:S233–38
62. Young A. 2005. Inhibition of gastric emptying. *Adv. Pharmacol.* 52:99–121
63. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. 1994. Positional cloning of the mouse obese gene and its human homologue. *Nature* 372:425–32
64. Ahima RS, Osei SY. 2004. Leptin signaling. *Physiol. Behav*. 81:223–41
65. Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, et al. 1999. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA* 282:1568–75
66. Mori H, Hanada R, Hanada T, Aki D, Mashima R, et al. 2004. Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. *Nat. Med.* 10:739–43
67. Herzog H. 2003. Neuropeptide Y and energy homeostasis: insights from Y receptor knockout models. *Eur. J. Pharmacol*. 480:21–29
68. Ste Marie L, Luquet S, Cole TB, Palmiter RD. 2005. Modulation of neuropeptide Y expression in adult mice does not affect feeding. *Proc. Natl. Acad. Sci. USA* 102:18632–37
69. Cone RD. 2005. Anatomy and regulation of the central melanocortin system. *Nat. Neurosci*. 8:571–78
70. O'Rahilly S, Yeo GS, Farooqi IS. 2004. Melanocortin receptors weigh in. *Nat. Med*. 10:351–52

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

71. Kuo JJ, Silva AA, Hall JE. 2003. Hypothalamic melanocortin receptors and chronic regulation of arterial pressure and renal function. *Hypertension* 41:768–74
72. Nordheim U, Nicholson JR, Dokladny K, Dunant P, Hofbauer KG. 2006. Cardiovascular responses to melanocortin 4-receptor stimulation in conscious unrestrained normotensive rats. *Peptides* 27:438–43
73. Wessells H, Blevins JE, Vanderah TW. 2005. Melanocortinergic control of penile erection. *Peptides* 26:1972–77
74. Diamond LE, Earle DC, Rosen RC, Willett MS, Molinoff PB. 2004. Double-blind, placebo-controlled evaluation of the safety, pharmacokinetic properties and pharmacodynamic effects of intranasal pt-141, a melanocortin receptor agonist, in healthy males and patients with mild-to-moderate erectile dysfunction. *Int. J. Impot. Res.* 16:51–59
75. Balthasar N, Dalgaard LT, Lee CE, Yu J, Funahashi H, et al. 2005. Divergence of melanocortin pathways in the control of food intake and energy expenditure. *Cell* 123:493–505
76. Wynne K, McGowan B, Bloom S. 2005. Appetite control. *J. Endocrinol.* 184:291–318
77. Holst JJ. 2006. Glucagon-like peptide-1: from extract to agent. The Claude Bernard Lecture, 2005. *Diabetologia* 49:253–60
78. Park A, Bloom SR. 2004. Peptides and obesity: the PYY3–36 story. *Regul. Pept.* 119:1–2
79. Boggiano MM, Chandler PC, Oswald KD, Rodgers RJ, Blundell JE, et al. 2005. PYY3–36 as an antiobesity drug target. *Obes. Rev.* 6:307–22
80. Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, et al. 2003. Inhibition of food intake in obese subjects by peptide YY3–36. *N. Engl. J. Med.* 349:941–48
81. Ueno H, Yamaguchi H, Kangawa K, Nakazato M. 2005. Ghrelin: a gastric peptide that regulates food intake and energy homeostasis. *Regul. Pept.* 126:11–19
82. Cummings DE, Foster-Schubert KE, Overduin J. 2005. Ghrelin and energy balance: focus on current controversies. *Curr. Drug Targets* 6:153–69
83. Holst B, Schwartz TW. 2006. Ghrelin receptor mutations—too little height and too much hunger. *J. Clin. Invest.* 116:637–41
84. Harper ME, Dent R, Tesson F, McPherson R. 2004. Targeting thermogenesis in the development of antiobesity drugs. See Ref. 127, pp. 363–83
85. Collins S, Cao W, Robidoux J. 2004. Learning new tricks from old dogs: beta-adrenergic receptors teach new lessons on firing up adipose tissue metabolism. *Mol. Endocrinol.* 18:2123–31
86. Yanagisawa T, Sato T, Yamada H, Sukegawa J, Nunoki K. 2000. Selectivity and potency of agonists for the three subtypes of cloned human beta-adrenoceptors expressed in Chinese hamster ovary cells. *Tohoku J. Exp. Med.* 192:181–93
87. Boss O, Hagen T, Lowell BB. 2000. Uncoupling proteins 2 and 3: potential regulators of mitochondrial energy metabolism. *Diabetes* 49:143–56
88. Chan CB, Saleh MC, Koshkin V, Wheeler MB. 2004. Uncoupling protein 2 and islet function. *Diabetes* 53:S136–42

89. Hesselink MK, Mensink M, Schrauwen P. 2003. Human uncoupling protein-3 and obesity: an update. *Obes. Res.* 11:1429–43
90. Lafontan M. 2005. Fat cells: afferent and efferent messages define new approaches to treat obesity. *Annu. Rev. Pharmacol. Toxicol.* 45:119–46
91. Nawrocki AR, Scherer PE. 2005. Keynote review: the adipocyte as a drug discovery target. *Drug Discov. Today* 10:1219–30
92. Boss O, Bergenhem N. 2006. Adipose targets for obesity drug development. *Expert Opin. Ther. Targets* 10:119–34
93. Matsuzawa Y. 2006. Therapy insight: adipocytokines in metabolic syndrome and related cardiovascular disease. *Nat. Clin. Pract. Cardiovasc. Med.* 3:35–42
94. Bouskila M, Pajvani UB, Scherer PE. 2005. Adiponectin: a relevant player in PPARgamma-agonist-mediated improvements in hepatic insulin sensitivity? *Int. J. Obes.* 29:S17–23
95. Arner P. 2005. Resistin: yet another adipokine tells us that men are not mice. *Diabetologia* 48:2203–5
96. Cohen P, Friedman JM. 2004. Leptin and the control of metabolism: role for stearoyl-CoA desaturase-1 (SCD-1). *J. Nutr.* 134:2455S–63
97. Chen HC, Farese RVJ. 2005. Inhibition of triglyceride synthesis as a treatment strategy for obesity. Lessons from DGAT1-deficient mice. *Arterioscler. Thromb. Vasc. Biol.* 25:482–86
98. Heffernan M, Summers RJ, Thorburn A, Ogru E, Gianello R, et al. 2001. The effects of human GH and its lipolytic fragment (AOD 9604) on lipid metabolism following chronic treatment in obese mice and beta(3)-AR knock-out mice. *Endocrinology* 142:5182–89
99. Kolonin MG, Saha PK, Chan L, Pasqualini R, Arap W. 2004. Reversal of obesity by targeted ablation of adipose tissue. *Nat. Med.* 10:625–32
100. Rajala MW, Scherer PE. 2003. Minireview: The adipocyte—at the crossroads of energy homeostasis, inflammation, and atherosclerosis. *Endocrinology* 144:3765–73
101. Maggard MA, Shugarman LR, Suttorp M, Maglione M, Sugerman HJ, et al. 2005. Meta-analysis: surgical treatment of obesity. *Ann. Intern. Med.* 142:547–59
102. Wolfe BM, Morton JM. 2005. Weighing in on bariatric surgery: procedure use, readmission rates, and mortality. *JAMA* 294:1960–63
103. Cummings DE, Overduin J, Foster-Schubert KE. 2004. Gastric bypass for obesity: mechanisms of weight loss and diabetes resolution. *J. Clin. Endocrinol. Metab.* 89:2608–15
104. Leibel RL, Rosenbaum M, Hirsch J. 1995. Changes in energy expenditure resulting from altered body weight. *N. Engl. J. Med.* 332:621–28
105. Lambert PD, Anderson KD, Sleeman MW, Wong V, Tan J, et al. 2001. Ciliary neurotrophic factor activates leptin-like pathways and reduces body fat, without cachexia or rebound weight gain, even in leptin-resistant obesity. *Proc. Natl. Acad. Sci. USA* 98:4652–57
106. Ettinger MP, Littlejohn TW, Schwartz SL, Weiss SR, McIlwain HH, et al. 2003. Recombinant variant of ciliary neurotrophic factor for weight loss in obese adults: a randomized, dose-ranging study. *JAMA* 289:1826–32

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

107. Kokoeva MV, Yin H, Flier JS. 2005. Neurogenesis in the hypothalamus of adult mice: potential role in energy balance. *Science* 310:679–83
108. Horvath TL. 2005. The hardship of obesity: a soft-wired hypothalamus. *Nat. Neurosci*. 8:561–65
109. Crampin EJ, Halstead M, Hunter P, Nielsen P, Noble D, et al. 2004. Computional physiology and the Physiome Project. *Exp. Physiol.* 89:1–26
110. Guyton AC, Montani JP, Hall JE, Manning RDJ. 1988. Computer models for designing hypertension experiments and studying concepts. *Am. J. Med. Sci*. 295:320–26
111. Takahashi N, Hagaman JR, Kim HS, Smithies O. 2003. Minireview: computer simulations of blood pressure regulation by the renin-angiotensin system. *Endocrinology* 144:2184–90
112. Noble D. 2002. Modeling the heart—from genes to cells to the whole organ. *Science* 295:1678–82
113. Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, et al. 2005. Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N. Engl. J. Med.* 353:2111–20
114. Flodmark CE, Marcus C, Britton M. 2006. Interventions to prevent obesity in children and adolescents: a systematic literature review. *Int. J. Obes*. 30:579–89
115. Summerbell CD, Waters E, Edmunds LD, Kelly S, Brown T, Campbell KJ. 2005. Interventions for preventing obesity in children. *Cochrane Database Syst. Rev.* 3:CD001871.pub2.DOI:10.1002/14651858.CD001871.pub2
116. Wadden TA, Butryn ML, Byrne KJ. 2004. Efficacy of lifestyle modification for long-term weight control. *Obes. Res*. 12:151S–62
117. Hofbauer KG, Nicholson JR. 2006. Pharmacotherapy of obesity. *J. Exp. Clin. Endocrinol. Diabetes*. In press
118. Heilbronn LK, de Jonge L, Frisard MI, DeLany JP, Larson-Meyer DE, et al. 2006. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. *JAMA* 295:1539–48
119. Hansen BC, Bodkin NL, Ortmeyer HK. 1999. Calorie restriction in nonhuman primates: mechanisms of reduced morbidity and mortality. *Toxicol. Sci*. 52:56–60
120. Blanc S, Schoeller D, Kemnitz J, Weindruch R, Colman R, et al. 2003. Energy expenditure of rhesus monkeys subjected to 11 years of dietary restriction. *J. Clin. Endocrinol. Metab.* 88:16–23
121. Dulloo AG. 2005. A role for suppressed skeletal muscle thermogenesis in pathways from weight fluctuations to the insulin resistance syndrome. *Acta Physiol. Scand*. 184:295–307
122. Ingram DK, Anson RM, de Cabo R, Mamczarz J, Zhu M, et al. 2004. Development of calorie restriction mimetics as a prolongevity strategy. *Ann. N.Y. Acad. Sci.* 1019:412–23
123. Bordone L, Guarente L. 2005. Calorie restriction, SIRT1 and metabolism: understanding longevity. *Nat. Rev. Mol. Cell Biol*. 6:298–305
124. Sinclair DA, Guarente L. 2006. Unlocking the secrets of longevity. *Sci. Am*. 294:48–51, 54–57

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

125. Wood JG, Rogina B, Lavu S, Howitz K, Helfand SL, et al. 2004. Sirtuin activators mimic caloric restriction and delay ageing in metazoans. *Nature* 430:686–89
126. Lin SJ, Ford E, Haigis M, Liszt G, Guarente L. 2004. Calorie restriction extends yeast life span by lowering the level of NADH. *Genes Dev*. 18:12–16
127. Hofbauer KG, Keller U, Boss O, ed. 2004. *Pharmacotherapy of Obesity. Options and Alternatives*. Boca Raton, FL: CRC Press

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Farooqi IS, O'Rahilly S. 2005. Monogenic obesity in humans. *Annu. Rev. Med.* 56:443–58

Cruz ML, Shaibi GQ, Weigensberg MJ, Spruijt-Metz D, Ball GDC, Goran MI. 2005. Pediatric obesity and insulin resistance: Chronic disease risk and implications for treatment and prevention beyond body weight modification. *Annu. Rev. Nutr.* 25:435–68

Crookes PF. 2006. Surgical treatment of morbid obesity. *Annu. Rev. Med.* 57:243–64

Reaven GM. 2005. The insulin resistance syndrome: Definition and dietary approaches to treatment. *Annu. Rev. Nutr.* 25:391–406

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

Annual Review of Pharmacology and Toxicology

Volume 47, 2007

Contents

Annu. Rev. Pharmacol. Toxicol. 2007.47:565-592.

Indexes

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