ANTIOBESITY DRUGS

1. Medical and Economic Aspects of Obesity

Obesity is an increasingly prevalent, complex disease with multiple etiologies and profound medical consequences. In addition to being a cosmetic problem, overweight and obesity are associated with an enhanced likelihood of developing chronic conditions including hypertension, hyperlipidemia, coronary heart disease, diabetes, cancer, gall bladder disease, and arthritis (1). In the 1990s, an

estimated 55% of the U.S. adult population was either overweight [body mass index] (BMI) 25–29.9] or obese (BMI ≥30) (2,3) and ∼280,000–325,000 deaths were attributed to obesity annually (4). The U.S. public spends heavily on weight control products and services. For example, in 1990, the total market including diet drinks, low calorie foods, meal replacements, health clubs, weight loss clinics, medically supervised weight loss programs, and various over-the-counter remedies amounted to $45.8 billion. In contrast, by 1998 prescription drugs accounted for only $184 million, or ∼6% (5).

To define the obese state in a clinical setting, it is necessary to have a means of estimating the amount of adipose (fat) tissue relative to lean body mass. Large clinical studies typically employ measures of skin-fold thickness, waist/hip ratio, waist circumference, or more commonly, BMI=(weight in kg)/(height in m)^2] as a quantitative measure of obesity (6). Commonly accepted classifications for stages of obesity based on BMI are summarized in Table (1) (7).

In addition to the obvious role of the environment, there is a significant predisposing genetic component to obesity as indicated in a number of twin and adoption studies (8,9). Although there are rare cases of extreme obesity that can be ascribed to a defect in a single gene, a considerable body of evidence supports a polygenic contribution to most forms of obesity. Intense efforts are under way to identify candidate genes, since it is estimated that genetic factors account for 70% of the variation in weight between individuals (10,11). Obesity is rare in many third world populations until the people become westernized, adopting energy-rich diets and sedentary lifestyles. These individuals may be adapted to endure episodes of scarcity and are able to utilize food very efficiently. Those harboring these "thrifty genes" may be more prone to developing obesity when given access to abundant nutrients.

Individuals with a BMI in the range of 25–30 should begin a diet and exercise program with behavior modification. Those with at least one risk factor, such as a family history of heart disease, smoking, or high blood pressure, should be started on pharmacological intervention. People with a higher BMI, and particularly those with a BMI of >40, are candidates for increasingly aggressive treatment (12). An important consideration is the location of the excess fat. Although obesity is a serious health risk factor for both sexes, the abdominal or android pattern of fat distribution typical of overweight males carries a higher risk of life-threatening complications than the gluteal or gynoid fat distribution typical of overweight females (13,14).

Table 1. **Weight Classification by BMI**[a]

NHLBI[b] Terminology	BMI, kg/m^2	WHO[c] classification
underweight	<18.5	underweight
normal	18.5–24.9	normal range
overweight	25.0–29.9	preobese
obesity class 1	30.0–34.9	obese class 1
obesity class 2	35.0–39.9	obese class 2
obesity class 3	>40.0	obese class 3

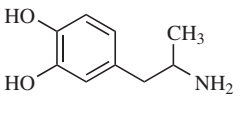
[a] Reproduced with permission from Ref. 2.
[b] National Heart, Lung and Blood Insitute.
[c] World Health Organization.

The balance between energy intake and energy expenditure is finely regulated in most people, and they maintain relatively consistent body weights for long periods despite variations in their day-to-day nutrient consumption. Although the mechanism is not understood at present, individuals may have a metabolic set point that provides a homeostatic drive toward weight maintenance. For many obese patients, this set point is inappropriately high and favors an increase in metabolic efficiency and restoration of body mass (15,16) after weight loss. One attractive approach to treating obesity would be to find a way to reset this metabolic set point to a lower BMI.

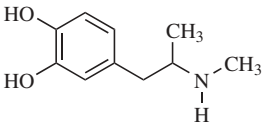
2. Treatment of Obesity

2.1. Introduction. Obesity is a difficult condition to treat. Dietary restriction of caloric intake is the first line therapy and is optimally combined with an exercise program to promote loss of fat relative to lean body mass (12). Drug treatments that help to suppress appetite, increase energy expenditure, or decrease fat absorption are available and may be beneficially used in conjunction with a comprehensive weight loss program. For the extremely obese (BMI >40), gastric by pass surgery has shown promise (17). The majority of formerly obese patients eventually regain their excess weight lost through diet, and thus a truly successful program must include long-term behavior modification.

2.2. Anorectics (Appetite Suppressants). Appetite suppressants are widely used as an adjunct to dietary restriction, and sympathomimetic amines have traditionally been used for this purpose. The sympathetic or adrenergic nervous system operates in juxtaposition to the parasympathetic nervous system to maintain homeostasis in response to physical activity and physical or psychological stress. Sympathomimetic neurotransmission is generally mediated by norepinephrine (1) released from presynaptic storage granules upon stimulation. A second endogenous sympathomimetic agent, epinephrine (2) is released systemically from the adrenal glands during emergencies as part of the "fight or flight" response. A large variety of peripheral organ functions are affected by the sympathetic nervous systems including heart rate, cardiac contractile force, blood pressure, bronchopulmonary tone, and metabolism. In the central nervous system (CNS), sympathetic nervous stimulation results in increases in wakefulness and psychomotor activity, and reduction of appetite (18).



(1)



(2)

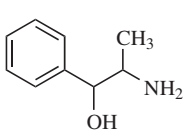
Compounds structurally related to the endogenous sympathomimetic amines have classically been employed as appetite suppressants. These agents, of which amphetamine is the prototypical example, generally retain the phenethylamine but lack the catechol moiety present in 1 and 2. As a consequence,

they are well absorbed after oral administration and readily distribute into the central nervous system, where they exert their anorectic effects at hypothalamic appetite control centers. A component of their efficacy in promoting weight loss may be an increase in metabolic rate through stimulation of thermogenesis or physical activity.

These compounds act primarily by indirect mechanisms involving displacement of norepinephrine from presynaptic nerve storage vesicles or by prevention of its reuptake rather than by a direct effect at the receptor level (18). To a lesser extent, certain agents of this class affect dopaminergic or serotoninergic neurons. The overall pharmacological profile of members of the non-catecholaminergic sympathomimetic amine class depends on their individual tissue distribution and their precise mechanism of action. While they vary in degree, all members of this group share similar liabilities of cardiovascular side effects, the potential for CNS stimulation, the development of tolerance, and abuse potential. Introduction of an oxygen atom on the β-carbon of the side chain tends to reduce their CNS stimulant properties without decreasing their anorectic activity. Following the Federal Controlled Drug Act of 1970, many of these drugs were classified into one of five schedules in decreasing order of their abuse potential. The Controlled Substances Act of 1970 classified drugs into schedules depending on their abuse potential: Schedule II, high potential for abuse; Schedule III, some potential for abuse, Schedule IV, low potential for abuse.

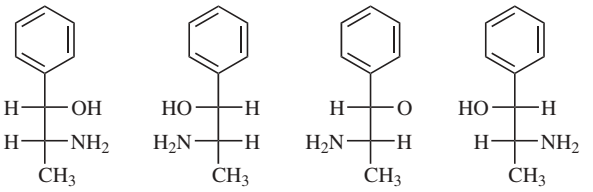
Phenylpropanolamine. As indicated in Table 2, phenylpropanolamine is the one member of this class, that is available over the counter (OTC). It is present in a number of common diet aids and nasal decongestants with such well known names as Dexatrim, Accutrim, Contac, and Dimetapp. Since it has two asymmetric carbon atoms, phenylpropanolamine has four theoretically possible stereoisomers. The compound sold as phenylpropanolamine in the United States is (±)-norephedrine and consists of equal amounts of D-(−)- and L-(+)-norephedrine 3 and 4, respectively, which are shown in the Fisher projection to illustrate the erythro relationship between their amino and hydroxyl groups. The diastereomers with the opposite (threo) relationship between these groups are referred to as D-(−)- and L-(+)-norpseudoephedrine, 5 and 6, respectively. In Europe and Australia the material sold as cathine and often referred to as phenylpropanolamine in the literature, is 6. Although also used as an anorectic agent, 6 has greater CNS stimulant effects and a different toxicological profile from (±)-norephedrine (19). This situation has led to considerable confusion in the literature

Table 2. **Phenylpropanolamine**



phenylpropanolamine CASRN: [37577-28-9] (base)
hydrochloride CASRN: [154-41-6] (hydrochloride)
[R*,S*]-(±)-α-(1-aminoethyl)benzenemethanol hydrochloride
formula: $C_9H_{13}NO$ mol.wt.: 151.21
brand name: Accutrim manufacturer: Novartis Consumer Health
brand name: Dexatrim manufacturer: Thompson Medical
dose: 75 mg 1×daily

over side effects and efficacy of individual isomers.



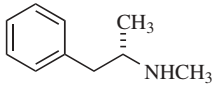
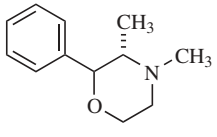
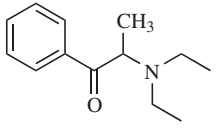
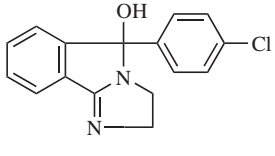
(3) (4) (5) (6)

(±)-Norephedrine is pharmacologically similar to other indirect acting sympathomimetic amines, but it has little CNS stimulant activity. After high doses, it does affect peripheral α- and β-adrenergic sympathetic receptors, resulting in cardiovascular symptoms, but these are generally not troublesome at normal clinical doses. Its efficacy as a nasal decongestant is related to vasoconstrictor effects on blood vessels in the nasopharynx. (±)-Norephedrine is well absorbed after oral administration and is excreted largely unchanged in the urine over the course of 24 hrs. A number of clinical trials have focused on its efficacy in appetite suppression, and these have been summarized (20–23). Because most of these trials were of short duration and rarely were run in comparison with other anorectic drugs, it is difficult to assess the relative utility of (±)-norephedrine with respect to the pharmacologically related prescription drugs in the longer term treatment of obesity. Informal surveys indicate the product is largely used to assist in short-term weight loss programs following a period of unusual weight gain, as might occur, for example, following a vacation. In October 2000, in light of a Yale University study indicating that use of phenylpropanolamine slightly increases the risk of hemorrhagic stroke in women, the Food and Drug Administration (FDA) advisory committee voted 13–0 that phenylpropanolamine cannot be classified as safe. Further action on the part of the FDA banning this drugs from OTC products is likely (24).

Sympathomimetic Amines. The sympathomimetic amines listed in Table 3 are related to amphetamine and are still available on the U.S. market for use in weight loss programs, although their sales are minimal (<$1 million/yr). These include methamphetamine (Desoxyn Gradumet, Schedule II (20), phendimetrazine (Bontril, Schedule III), diethylproprion hydrochloride (Tenuate, Schedule IV), and mazindol (Sanorex, Schedule IV). These compounds are indicated for short-term use when other therapies have been unsuccessful. They are relatively effective over the course of at least several weeks, and although tolerance is considered to be a problem, it does not always occur.

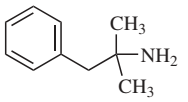
Phentermine. Phentermine (Fastin, Adipex-P, Ionamin), a sympathomimetic amine with low abuse potential, is still prescribed widely for the short-term treatment of obesity. It was launched in 1959 and came into widespread use in the mid-1990s in a combination with fenfluramine commonly known as fen-phen. By itself, phentermine acts at dopaminergic and adrenergic neurons to exert its anorexic effect (23,25,26). Since it is also an inhibitor of the enzyme monoamine oxidase -A (MAO-A), which plays an important role in the clearance of serotonin following its release from presynaptic neurons (27), an enhancement of

Table 3. **Sympathomimetic Amines**

	methamphetamine hydrochloride	CASRN: [537-46-2] (base) CASRN: [51-57-0] (hydrochloride)
	(*S*)-*N*,α-dimethyl benzeneethanamine hydrochloride formula: $C_{10}H_{15}N$	mol. wt: 149.23 (base) mol. wt. 185.69 (hydro-chloride)
	brand name: Desoxyn Gradumet dose: 5, 10 or 15 mg 1×daily Schedule II controlled substance	manufacturer: Abbott Pharmaceuticals
	phendimetrazine hydrochloride	CASRN: [634-03-7] (base) CASRN: [50-58-8] (tartrate)
	(2*S*,3*S*)-3,4-dimethyl-2- phenylmorpholine Tartrate formula: $C_{12}H_{17}NO$	mol. wt. 191.27 (base) mol. wt. 341.36 (tartrate)
	brand name: Bontril and Bontril Slow Release dose: 105 mg, 1×daily (slow release formulation equivalent to 35 mg, 3×daily Schedule III controlled substance	manufacturer: Carnick Laboratories
	diethylpropion hydrochloride	CASRN: [90-84-6] (base) CASRN: [139-80-5] (hydrochloride)
	2-(diethylamino)-1-phenyl-1-propanone hydrochloride formula: $C_{13}H_{19}NO$	mol wt. 205.30 (base) mol. wt. 241.78 (hydro-chloride)
	brand name: Tenuate dose: 25 mg 3×daily or 75 mg of Tenuate Dospan 1×daily	manufacturer: Aventis[a]
	mazindol	CASRN: [22232-71-9] (base) CASRN: [58535-70-9] (hydrochloride)
	5-(4-chlorophenyl)-2,5- dihydro-3*H*-imidazo[2,1-a] isoindol-5-ol formula: $C_{16}H_{13}ClN_2O$	mol. wt. 284.74 (base) mol. wt. 321.20 (hyrdro-chloride)
	brand name: Sanorex dose: 1–3 mg 1×daily	manufacturer: Novartis

[a] Formerly Hoechst Marion Roussel

Table 4. **Phentermine**

	generic name: phentermine hydrochloride	CASRN: [122-09-8] (base)
		CASRN: [1197-21-3] (hydrochloride)
	α,α-dimethylbenzeneethan amine hydrochloride	
	formula: $C_{10}H_{15}N$	mol. wt. 149.23 (base)
		mol. wt. 185.69 (hydrochloride)
	brand name: Adipex-Pr[a]	manufacturer: Gate Pharmaceuticals
	brand name: Fastin[a]	manufacturer: Smith Kline Beecham Pharmaceuticals
	brand name: Ionamin[b]	manufacturer: Medeva Pharmaceuticals
	dose: 15–30 mg 1×daily	

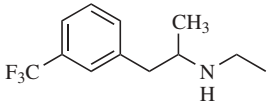
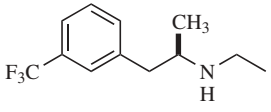
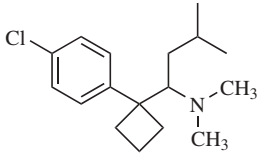
[a] Contains 30 mg of phentermine hydrochloride equiv to 24 mg of the free base.
[b] Contains either 15 or 30 mg of phentermine complexed with a cation-exchange resin.

serotonergic neurotransmission may also be a component of its activity. In rats, the compound is extensively metabolized by parahydroxylation (28), whereas in humans the 4-hydroxy derivative is only a minor metabolite (29). The results of several small clinical trials of up to 6-months duration have been summarized and indicate that the drug promotes a statistically significant weight loss with mild side effects related to its CNS stimulatory activity (25). The relatively low rate of metabolism of the drug in humans accounts for its long duration of action. Although sales of phentermine in the United States have fallen since the withdrawal of fenfluramine, it is still widely used, and in 1999 there were ∼4 million prescriptions written with sales amounting to $54 million (30). Table 4 gives some basic data on phentermine.

Fenfluramine and Dexfenfluramine. Fenfluramine (Pondimin) is a racemate; the (+)-enantiomer, dexfenfluramine (Redux), is twice as effective as the racemate as an appetite suppressant and has been shown in clinical trials to be relatively free of side effects (31–32). Rat studies indicate that in contrast to amphetamine, which tends to delay the onset of meals and decrease protein intake, fenfluramine decreases the rate of eating and promotes early meal termination with no effect on meal pattern or nutrient selection (33–34). Fenfluramine was approved in the United States for the treatment of obesity in 1973, and dexfenfluramine was approved in 1996. A key paper by Weintraub (35) summarizing the results of a 4-year trial of a combination with fenfluramine with phentermine in patients sparked a dramatic popularization of the "fen-phen" combination; an estimated 18 million patients were treated with fen-phen between 1992 and 1997 (36). Reports of primary pulmonary hypertension (37) and valvular heart disease (38–40) associated with drug therapy prompted the withdrawal of fenfluramine and dexfenfluramine (Table 5) from the world markets in 1997 and resulted in one of the largest product liability lawsuits ever. In 1999 and 2000, American Home Products took a $12.25 billion charge against earnings to cover the costs of the settlement (41). Possible explanations for these rare side effects involving local serotonergic effects on the heart and lungs have been proposed (42), but the cause is still under investigation (43).

Sibutramine. Sibutramine (Meridia) is an inhibitor of both norepinephrine and serotonin uptake with a much weaker effect on dopamine

Table 5. **Mixed Sympathomimetic and Serotonergic Agents**

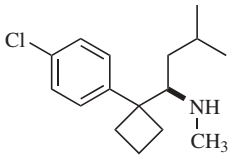
	generic name: fenfluamine hydrochloride *N*-ethyl-α-methyl-(3-trifluoromethyl)benzeneethan amine hydrochloride formula: $C_{12}H_{16}F_3N$ brand name: Pondimin dose: 75 mg 1×daily	CASRN: [458-24-2] (base) CASRN: [404-82-0] (hydrochloride) mol. wt.: 231.26 (base) mol. wt.: 267.72 (hydrochloride) manufacturer: American Home Products[a]
	generic name: dexfenfluramine formula: $C_{12}H_{16}F_3N$ brand name: Redux (*R*)-*N*-ethyl-α-methyl-(3-trifluoromethyl)benzeneeth anamine hydrochloride	CASRN: [37577-24-5] (base) CASRN: [3616-78-2] (hydrochloride) mol. wt.: 231.26 (base) mol. wt.: 267.72 (hydrochloride) manufacturer: American Home Products[a]
	generic name: sibutramine hydrochloride monohydrate 1-(4-chlorophenyl)-*N*,*N*-dimethyl-α-(2-methylpropyl)cyclobutanemethanamine hydro chloride hydrate formula: $C_{17}H_{28}ClN$ brand name: Meridia dose: 10–15 mg, 1×daily	CASRN: [106650-56-0] (base) CASRN: [12494-59-9] (hydrochloride hydrate) mol. wt.: 279.86 (base) mol. wt. 334.33 (hydrochloride hydrate) manufacturer: Knoll Phamaceuticals

[a] Fenfluramine and Dexfenfluramine were withdrawn from the world wide markets in 1997.

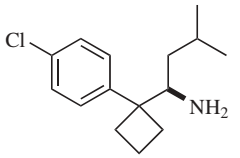
reuptake (44,45). It affects appetite more consistently than selective serotonin reuptake inhibitors such as fluxetine, which are relatively ineffective in promoting weight loss (46). Results of feeding studies in rats treated simultaneously with sibutramine and various selective adrenergic and serontonin receptor antagonists are consistent with the reuptake inhibition mechanism and indicate that a combination of effects at adrenergic α_1 and β_1 and serotonergic 5-$HT_{2a/2c}$ receptors are responsible for its hypophagic activity (47). Sibutramine is also capable of blunting the homeostatic decrease in energy expenditure that normally accompanies weight loss (48). It was introduced in the U.S. market in 1998 after extensive clinical trials that demonstrated a modest effect on weight loss after treatments ranging from 2 months to 1 yr. Side effects were mainly increased blood pressure, dry mouth, and constipation. According to the summary provided in the *Physician's* Desk Reference, ~60% of patients who initially responded to sibutramine treatment with a weight loss of 4 lb in the first month were able to achieve a 5% overall weight loss after 6 months (49).

The bioavailability of sibutramine is 77% in humans and it undergoes extensive first-pass metabolism to two primary demethylated metabolites, which are largely responsible for its biological activity. Thus, the parent drug has a clearance rate of 1760 L/h and a $t_{1/2}$ of 1.1 h, whereas the *N*-desmethyl metabolite, (7) and the *N*,*N*-didesmethyl metabolite, (8) have terminal elimination half-lives of 14 and 16 h, respectively. The metabolites reach a steady state after 4 days of dosing (48). Sibutramine is racemic. The major metabolites are derived from the (*R*)-isomer, as demonstrated recently by total synthesis and X-ray crystallographic analysis, and are more potent anorectic agents than the corresponding (*S*)-isomers (50,51).

There were 1.3 million prescriptions for sibutramine in the United States during 1999 with total sales amounting to $102 million, a decrease over the corresponding numbers for 1998, the year of launch (30).



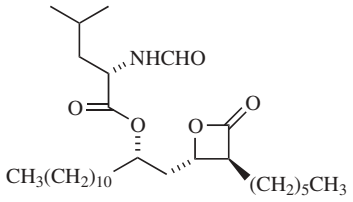
(**7**)



(**8**)

2.3. Lipid Adsorption Inhibitors. *Orlistat.* Dietary fat occurs largely in the form of triglycerides that must be hydrolyzed through the action of lipases, primarily pancreatic lipase, in the digestive tract prior to absorption. When maintenance or induction of weight loss is desired with a minimal impact on meal composition, an attractive approach to limiting caloric intake is to minimize the absorption of fat by inhibiting pancreatic lipase. Lipstatin is a pancreatic lipase inhibitor isolated from *Streptomyces toxytricini* (52,53). The corresponding tetrahydro derivative, orlistat (Xenical), has been shown to decrease fat absorption in mice, rats, and monkeys and to lower the rate of body weight gain in rats

Table 6. **Orlitstat**



generic name: Orlistat
CASRN: [96829-58-2]
N-formyl-*L*-leucine (1*S*)-1-[[(2*S*,3*S*)-3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester
formula: $C_{29}H_{53}NO_5$
mol. wt.: 495.73
brand name: Xenical
manufacturer: Hoffmann-La Roche Inc
dose: 120 mg 3×daily at meal times

on a high calorie diet (54–56). Its complex structure, combining a δ-lactone with four stereocenters has inspired a number of total syntheses (57–63).

In humans, a 120-mg oral dose of orlistat prior to a meal inhibits 30% of fat absorption. When administered to patients for up to 1 yr in conjunction with a reduced-calorie diet, significantly more of drug-treated patients than placebo-treated controls achieved a 5–10% weight loss. Patients who achieved weight loss during 1 yr of therapy and were maintained on orlistat for a second year were able to maintain their weight loss in the absence of strict dietary control (62). In a study of adult-onset diabetic subjects, 1 yr of orlistat treatment led to the expected weight loss accompanied by improvements in fasting glucose, low density lipoprotein (LDL) levels, and HbA1c (64, 65).

The drug acts locally in the gastrointestinal (GI) tract to reversibly inhibit lipases through attack of a lipase serine hydroxyl group on the γ-lactone carbonyl to give an inactivated acyl enzyme. Less than 2% of an oral dose is absorbed, and systemic side effects are virtually unknown. The side effects, which do occur, are a consequence of its mechanism of action and relate to the presence of excess fat in the GI tract. These symptoms include occasional oily stools, flatus with discharge, and fecal urgency. These symptoms are generally mild and decrease in frequency with continued dosing.

Orlistat (Table 6) was introduced to the U.S. market in April 1999 and is the first marketed product to act at the level of fat absorption. Approximately 1.5 million prescriptions were written during its first 8 months on the market, and sales were $146 million (30).

3. Future Developments

As noted, there is a significant unmet medical need for better modalities for the management of overweight and obesity together with their consequent morbidity. The size of the patient population in developed countries, and the staggering direct and indirect costs, have prompted an intense effort on the part of academic as well as pharmaceutical company laboratories to understand the driving forces governing nutrient absorption, satiety, and energy utilization. A key stimulus for this work was the 1994 discovery of the protein leptin, a 167 amino acid hormone produced in mammalian fat tissue (66) and released to the general circulation as

a function of the rate of glucose utilization (67). Leptin signaling is an important determinant of feeding behavior; mutations in the genes coding for leptin or its receptor in both mouse and hummans (68–70) lead to profound hyperphagia and obesity. Circulating leptin levels are proportional to overall adipose tissue mass but decrease markedly during fasting as a component of energy homeostasis. Research into the central pathways mediating leptin's role has substantially advanced our understanding of the mechanisms involved in appetite regulation.

3.1. Centrally Acting Drugs. Concentrated in the arcuate nucleus in the hypothalamus, leptin receptors mediate both inhibitory and stimulatory signals, projecting into the lateral hypothalamic/perifornical areas and paraventricular nucleus, respectively, to inhibit food intake (71). Clinical trials of leptin itself as an anorectic agent were disappointing (72); however, investigation of neurons expressing leptin receptors has led to the identification of several potential drug targets. So far, these include neuropeptide Y (NPY), Agouti-related peptide (AGRP), α-melanocyte-stimulating hormone (α-MSH), melanin-concentrating hormone (MCH), and orexins A and B. All these are peptidic neurotransmitters that interact with specific G-protein-coupled receptors (GPCR) to either stimulate (NPY, AGRP, orexins, MCH) or inhibit (α-MSH) food intake (73). Since GPCRs are generally excellent targets for small molecular weight drugs, it is likely that ligands for each will be discovered and tested in the near future.

Regeneron Pharmceuticals has recently reported the results of a phase II clinical trial of Axokine, a modified form of ciliary neurotrophic factor in 170 severely obese patients. Patients on 1 μg/kg lost an average of 8.9% of their body weight over the 12 weeks of dosing. The mechanism of action of this drug is not known, although there is speculation that it may be acting in the central nervous system. Phase III studies are planned for 2001 (74).

The effectiveness of serotonergic agents such as fenfluramine and sibutramine has prompted further investigation into novel serotonergic drugs with an emphasis on the 5-HT_{2c} subclass of receptors (75) with the anticipation that such drugs will be more selective, hence safer.

3.2. Peripherally Acting Drugs. Drugs that stimulate or block peripheral adrenergic receptors have been in widespread use for some time, e.g., as antihypertensives, antianginal agents, and bronchodilators. Detailed investigations with some of these led to the identification of the β_3-adrenergic receptor, which mediates catecholamine-induced lipolysis in brown adipose tissue leading to increases in thermogenesis. Compounds tested clinically to date were insufficiently selective for the human β_3-adrenergic receptor, but newer, more promising compounds are being evaluated (76,77).

The product of oxidative phosphorylation is adenosine triphosphate (ATP), which in turn is stoichiometrically coupled to various enzymatic pathways. The driving force for ATP synthesis is the oxidatively mediated transfer of protons across the inner mitochondrial membrane. In the late 1990s, uncoupling proteins (UCP-1, UCP-2, and UCP-3), were discovered that promote the leakage of protons across mitochondrial membranes, with consequent heat production (78, 79). One component of the thermogenic activity of β_3-agonists is their ability to promote increased expression of UCP-1 in brown adipose tissue. Other compounds that are capable of modulating the function of members of the uncoupling

protein family could be of interest for their ability to increase energy expenditure.

Protein tyrosine phosphatase-1b (PTP-1b) has become an exciting target for drug discovery based on a paper describing a mouse model in which the gene coding for PTP-1b was knocked out. These animals were healthy and fertile, had increased insulin sensitivity, and were surprisingly resistant to diet-induced obesity (80,81). These findings have prompted an intense search within the pharmaceutical industry for a small-molecule PTP-1b inhibitor that might serve to effectively treat both type 2 diabetes and obesity.

Locally released gut neuropeptides such as cholecystokinin (CCK) and glucagon-like peptide 1 (GLP-1) regulate food intake, probably through stimulation of vagal afferent fibers. Although tolerance and local side effects have limited development of CCK agonists, Glaxo Smith Kline has one in phase II clinical trial and reports preliminary indications of efficacy. On the other hand, both analogues of GLP-1 and compounds that inhibit its hydrolysis by endopeptidases are being developed clinically, although the efficacy of such agents has not yet been established (82,83).

Finally, compounds that inhibit fat absorption or utilization may be of interest. In addition to gut lipases, targets of such drugs could include the intestinal fatty acid transport protein FATP4 (84); the enzyme acyl coenzyme (Co-A): diacylglycerol transferase (DGAT), which catalyzes a key step in triglyceride synthesis (85); and the enzyme complex fatty acid synthetase, which is responsible for the conversion of malonyl Co-A to palmitoyl coenzyme-A. Inhibitors of the latter complex have been shown to cause profound weight loss in mice, possibly mediated in part by inhibition of the central release of neuropeptide Y (86).

4. Summary

The available appetite suppressants based on stimulation of the sympathetic nervous system have fallen out of favor for the treatment of morbid obesity with the exception of sibutramine. The introduction of the fat absorption inhibitor orlistat has offered a novel approach, free of the side effects and tolerance development associated with present centrally acting agents. Although drug treatment is not likely to replace diet and behavior modification for the control of obesity, the profound medical need combined with intensive research on both peripheral and central pathways involved in regulation of nutrient absorption, meal size, and energy utilization is certain to lead to new opportunities for the control and maintenance of desirable body weight. Ultimately, the measure of success in the overall treatment of obesity will be a reduction in the associated morbidity.

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