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REVIEW

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New approaches in the pharmacological treatment of obesity

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Summary Many new substances are currently being investigated for their usefulness in the pharmacotherapy of obesity. Most drugs interfere with monoamine neurotransmitter (serotonin, noradrenalin, dopamine and histamine) effects and act as an appetite suppressant. Other approaches are to primarily increase thermogenesis (e.g. β_3-adrenoceptor agonists), or to decrease fat absorption by inhibiting the pancreatic lipase (orlistat). New promising agents are substances that increase the effect of corticotropin releasing factor (CRF) or urocortin in the brain (CRF-binding protein ligand inhibitor) and a neuropeptide Y (NPY) Y_5 receptor antagonist. The clinical relevance of leptin in the therapy of obesity is probably limited, but can not be fully evaluated at the moment. As obesity has a multifactorial basis, all these substances have in common the fact that they can not cure obesity. They should only be used as an adjunct to classical strategies like diet and exercise in severe obesity. For developing new, perhaps even more specific pharmacological agents, further research is needed to understand the individually different genetic and physiological basis of obesity.

Key words Pharmacotherapy – obesity – appetite suppressant – thermogenesis

Introduction

Obesity is one of the major health problems in industrialized countries (e.g., (19)). It is often associated with chronic diseases like hyperlipidemia, hypertension, insulin resistance, and type II diabetes, and with increased risk of coronary heart diseases. Obese individuals also exhibit a higher prevalence of gallstone disease and several major cancers (for example breast and colon) than normal weight subjects (19, 21, 91, 101). Obesity together with its associated diseases accounts for about 3-7% of all health costs in the United States (22). The increasing prevalence of obesity in industrialized countries can be explained in part by a genetic susceptibility in combination with an abundance of highly palatable, energy dense food and low levels of physical activity (11, 12, 25, 73).

Estimates for the genetic contribution to the variance in body weight range from 20 to 70% (5, 16, 32, 39). About 20 genetic loci have been identified in humans that correlate with obesity (125), but very rarely are cases of human obesity the consequence of a single gene defect (120).

Obesity is defined as an excessive accumulation of body fat. In most countries a body mass index (BMI = body weight (kg)/ height (m^2)) of 25-30 is considered to be mild obesity, a BMI >30-35 as moderate, and a BMI >35 as severe obesity (25). Yet, not only the degree of body fat or obesity is important, but also fat distribution (e.g., (161)). Two different types of fat distribution can be distinguished: a) the abdominal, visceral, android, upper-body, or male type obesity and b) the gynoid, lower-body, or female type obesity (25). The risk of diabetes and cardiovascular diseases clearly increases with visceral obesity (161). Data from the Framingham study demonstrate how beneficial weight loss is: it was calculated that each 10% reduction in the body weight of men

would cause a 20% decrease in the incidence of coronary artery diseases. Unfortunately, there is a high level of failure in the therapeutic treatment of weight problems. Classical treatment strategies like dieting, behavioral modification, and exercise often fail to achieve long-term maintenance of weight loss (64). Only 5% of the patients treated with behavioral self-management of obesity achieved sustained weight loss, and the long-term success rate of a very low energy diet plus behavior training was about 10% (56). In recent years, more knowledge has been gained regarding the mechanism of energy homoeostasis and the complex nature of obesity (6). This should help to develop new pharmacotherapies to support the classical obesity management strategies. Yet, the use of an antiobesity drug can only be recommended if several conditions are met (Table 1). This review focuses on new pharmacological approaches in the treatment of obesity (Table 2). Because of the tremendous recent progress in this field, it is difficult to present a truly comprehensive overview of all drugs and substances that are now under investigation.

Drugs that interfere with monoamine neuro-transmitters

Serotoninergic drugs

It is well documented that serotonin (5-HT) inhibits food intake in mammals (133). The precursor of 5-HT is the amino acid L-tryptophan. The concentration of tryptophan in the brain determines the quantity of 5-HT produced (47). Tryptophan is transported from the blood stream into the brain by a specific carrier (127, 163). A high carbohydrate intake increases brain 5-HT (48) by increasing the tryptophan to LNAA (large neutral amino acid) ratio in the blood, and, hence uptake of it into the brain (9, 12, 49, 72). Originally it was assumed that 5-HT primarily inhibits carbohydrate intake (93, 163). Recently, this idea has been largely abandoned because it became clear that 5-HT strongly suppresses fat intake as well (14). In any case, it is undisputed that 5-HT is an important factor in the control of food intake, and many drugs that are used to treat obesity interfere with 5-HT metabolism. The most effective way, however, to alter energy intake is via agonism or antagonism of 5-HT receptors, not through alterations in serotonin synthesis.

Dexfenfluramine/fenfluramine

Dexfenfluramine stimulates 5-HT release into synaptic clefts, inhibits 5-HT reuptake into presynaptic neurons, and directly stimulates postsynaptic 5-HT receptors (40). The racemate fenfluramine contains the therapeutically active dextro-rotatory (+) stereoisomer of fenfluramine (dexfenfluramine = d-fenfluramine) and levofenfluramine (l-fenfluramine) (40, 46, 133). Dexfenfluramine administration (usually 2 x 15 mg daily) leads to reduced appetite (10) and body weight loss (12). Recent studies indicate that the hypophagic effect of dexfenfluramine (or of its active metabolite dexnorfenfluramine) is mainly caused by a direct activation of postsynaptic 5-HT_{1B} and/or 5-HT_{2C}-receptors (formerly termed 5-HT_{1C} receptor) (29, 36, 42, 60, 143). Most animal studies suggest that the 5-HT-receptor-mediated anorectic action occurs in the paraventricular nucleus of the hypothalamus, but 5-HT receptors in the caudal brainstem may also contribute to the dexfenfluramine anorexia (60). 5-HT may also act peripherally to induce satiety (133). Whether dexfenfluramine increases thermogenesis and energy expenditure is not yet clear. While it increased the thermic effect of food in rodents, it failed to do so in a trial with 30 obese subjects, even though it decreased food intake and body weight (89). In short-term (3 month) and also in long-term (12 month) clinical studies dexfenfluramine was more effective in reducing body weight than placebo (40). In a one year trial, the dexfenfluramine-treated group lost on average 9.8 kg, whereas the placebo group had an average body weight loss of 7.2 kg (62). In normal weight subjects fenfluramine decreased caloric intake

Table 1 Criteria that an ideal antiobesity drug should fulfill (28, 40, 63, 64)

- it has to be proven that the drug reduces body weight through a selective decrease in body fat stores with sparing of body protein
- it should prevent weight regain once a desirable body weight has been reached
- it should improve compliance with weight-reduction programs based on classical treatment strategies like diet and exercise
- any side effects must be tolerable and transient
- it should not have stimulant properties and an addictive potential
- it should have a greater effect in obese subjects than in lean subjects and should not cause significant weight loss in lean subjects
- it should produce favorable alterations in the disturbed metabolic profile, e.g., lower plasma concentrations of triglycerides, free fatty acids, insulin, and glucose, and therefore improve body weight-dependent diseases
- the mode of action should be known

Table 2 Drugs for the treatment of obesity (literature for dosage of the discussed agents: 30, 61, 91, 132)

Drug	Class and mechanism	Dosage (mg/day)	Comment
	serotoninergic agents		
dexfenfluramine/ fenfluramine	appetite suppressants; stimulate serotonin release into the brain synaptic clefts and also postsynaptic serotonin receptors; inhibit serotonin re-uptake	2*15 60-120	currently not on the market, because of unexplained cases of heart valve diseases in patients taking a combination of fenfluramine and phentermine
fluoxetine	appetite suppressant; inhibits serotonin re-uptake	40-60	after a treatment period of five month a plateauing of weight loss is reached
sibutramine	appetite suppressant and thermogenic agent; inhibits serotonin and noradrenalin re-uptake	10-15	FDA approval for obesity therapy; heart rate and blood pressure should be observed
	dopaminergic agents		
bromocriptine	appetite suppressant; dopamine D_2 agonist with serotonin modulating activity	1.6-2.4	only one study with 17 obese subjects
doprexine	appetite suppressant; conjugate of dopamine and the polyunsaturated fatty acid cis docosahexaenoic acid		tested only in animal studies
	adrenergic and noradrenergic agents		
diethylpropion	all agents are appetite suppressants; enhance acitivity of adrenalin and noradrenalin; increase sympathetic activity	75	diethylpropion, mazindol and phentermine are the adrenergic drugs mostly used by physicians in the United States to treat obesity so far
mazindol		1-3	
phentermine		15-30	
phenylpropanolamine		27-75	
ephedrine/caffeine combination	appetite suppressant and thermogenic agent; increases the noradrenalin action	20/200	heart rate and blood pressure should be observed
β_3-adreno-ceptor agonists	thermogenic agents; increase thermogenesis of brown adipose tissue and lipolysis in white adipocytes in rodents		specific evaluation only possible if selective agonists for human β_3-adrenoceptor are developed and tested in clinical trials
	histaminergic agents		
H_3 receptor antagonist	appetite suppressant; increases brain histamine level		tested only in animal studies
	neuropetides		
CRF binding protein	appetite suppressant; increases endogenous brain level of unbound corticotropin releasing factor (CRF) or urocortin		tested only in animal studies
ligand inhibitor	appetite suppressant; inhibits the NPY induced feeding behavior		
NPY Y_5 antagonist			tested only in animal studies
	enzyme inhibitor		
orlistat	gastrointestinal lipase inhibitor; reduces fat absorption	3*120	approval from the European Commission; FDA has granted approvability status
	adipose tissue-derived peptide		
leptin	reduces food intake and increases energy expenditure in laboratory animals		at the moment, the clinical relevance of leptin in obesity therapy can not be conclusively evaluated

when the volunteers consumed a low-carbohydrate lunch, but was ineffective in combination with a high carbohydrate lunch (49). This suggests that macronutrients influence the effect of fenfluramine. Besides its anorectic effect, dexfenfluramine administration improved glycemic control, reduced cholesterol and triglyceride levels, as well as systolic and diastolic blood pressure (9, 63), and atherogenic risk factors. Nevertheless, after discontinuation of dexfenfluramine treatment body weight and cardiovascular risk factors returned to baseline (9). In short-term studies, dexfenfluramine was better tolerated than ephedrine/caffeine and fluoxetine (40). The originally reported side effects of dexfenfluramine such as dry mouth, diarrhea, tiredness, and drowsiness are dose-dependent, mild, and transient, when the usual dose of 15 mg is administered twice a day. More recently, however, it was reported that dexfenfluramine might have a hazardous potential to produce pulmonary hypertension and neurotoxicity (9, 57, 75). On September 15 1997, the U.S. Food and Drug Administration (FDA) asked the manufacturers to voluntarily withdraw fenfluramine and dexfenfluramine from the market (46). The reason for this move was a report of 24 cases of heart valve disease in patients taking a combination of fenfluramine and phentermine (fen-phen) (9, 21, 29, 35, 75). In addition, closer examination of the echocardiograms of 291 patients who had received these drugs and did not have symptoms of heart disease revealed abnormal valve findings, primarily aortic regurgitation, in 30% of these patients. No such cases were reported in patients taking phentermine alone (46). Yet, it is not known whether dexfenfluramine itself or the combination of dexfenfluramine with phentermine caused this morphological and functional damage to cardiac valves (27).

Fluoxetine

Fluoxetine is a selective 5-HT reuptake inhibitor that binds only weekly to specific 5-HT receptors (36, 55). It is a common medication in the treatment of depression and bulimia nervosa. At a higher dose (common practice is 60 mg/d) it also reduces food intake and body weight (13, 90). In a study with rats fluoxetine decreased primarily fat intake and had little effect on carbohydrate intake (72). Placebo-controlled clinical studies demonstrated a weight reducing effect of fluoxetine (55, 56, 90, 162) comparable to that of dexfenfluramine and fenfluramine (36). However, after a treatment period of about five months a plateau was reached, and thereafter many patients regained weight despite continuing treatment (13, 55, 56). At the end of a 52-week study with obese patients the weight change between the fluoxetine and placebo groups did not differ (55). Thus, there might be differences between various types of serotoninergic drugs during long-term administration (13). Apart from the weight loss, fluoxetine seems to improve peripheral insulin sensitivity in obese non-insulin-dependent diabetics (100, 162). Reported side effects include asthenia, sweating, somnolence, nausea, tremor, and abnormal dreams (56, 162). Urdaneta et al. (150) showed that fluoxetine reduced amino acid absorption as shown for leucine. Consequently, chronical administration of fluoxetine might have an impact on nutritional status of obese patients (150). Other 5-HT re-uptake inhibitors are sertraline, femoxetine, and paroxetine (133). So far dexfenfluramine and fenfluramine were the most important 5-HTergic drugs. Since fluoxetine is not as effective as dexfenfluramine, it will presumably not substitute it. However, the new 5-HT and noradrenalin re-uptake inhibitor sibutramine, which will be discussed in the next section, might be an effective and more promising drug in the therapy of obesity.

Sibutramine

Sibutramine inhibits the re-uptake of 5-HT and noradrenalin (29, 66, 84), but has little effect on dopamine metabolism (13). Sibutramine and its active metabolite also have no effect on 5-HT or noradrenalin release and do not react with their receptors (84, 141). Sibutramine was originally developed for the therapy of depression. Whereas it failed to show antidepressant activity, it was observed that patients taking this preparation lost body weight (69, 141).

In several long-term studies (12 months), sibutramine reduced body weight compared to placebo. After 12 months the achieved weight loss was 5-6 kg compared with 2 kg in the placebo group, and after exclusion of non-responders the average weight loss was even 8 kg. The effect of sibutramine on body weight was dose-related with an optimal dose of 10 and 15 mg per day (91). In one study in rats, sibutramine reduced food intake more than the 5-HT and noradrenalin re-uptake inhibitors venlafaxine and duloxetine (84). Sibutramine did not only enhance satiety in rats, but also stimulated thermogenesis presumably via central activation of efferent sympathetic activity, which involved activation of β_3-adrenergic receptors (141).

In humans, sibutramine prevented the decline in 24 h energy expenditure that normally occurs in obese subjects on a low calorie diet (3). In addition, sibutramine appears to preferentially reduce visceral fat, as indicated by a significant decrease in the waist-to-hip ratio (153), and it appears to improve obesity-related risk factors like glucose intolerance, lipid parameters, and hyperuricaemia (154). Since sibutramine is a noradrenalin re-uptake inhibitor, it elevates systolic and diastolic blood pressure by a mean of 2 mmHg at a dose of 10-15 mg/d. In a placebo controlled study with mildly hypertensive obese patients, however, mean diastolic blood pressure fell in the placebo and in the sibutramine treated group. Therefore, the expected reduction of blood pressure by weight loss seems to exceed the blood pressure increasing effect of a noradrenalin re-uptake inhibitor (91). In another trial with

obese patients no significant change in blood pressure was observed, however, heart rate was increased. Other adverse events with sibutramine were dry mouth, constipation, and insomnia (66). As a consequence, blood pressure and heart rate should be carefully observed in patients receiving sibutramine (91). Sibutramine has recently received FDA approval for the treatment of obesity (29).

Dopaminergic drugs

Dopamine plays a major role in the regulation of food intake (33). In the nucleus accumbens, dopamine enhances response output and there it can induce eating. Dopamine release in this brain area is associated with pleasure and reward. Therefore, nutritional stimuli that increase dopamine in the nucleus accumbens become preferred stimuli. However, it is also well known that in the hypothalamus dopaminergic substances suppress appetite (76), and dopamine D_2 receptor antagonists enhance it (33). One of the most effective appetite suppressants is the dopaminergic and adrenergic agonist amphetamine. The addictive potential of amphetamine can be explained by its effect on the dopaminergic reward pathway of the brain (29, 33). Therefore, for the treatment of obesity it is necessary to develop drugs that interfere with dopamine metabolism without having an addictive potential.

Bromocriptine

One of the new dopamine agonists with anorectic activities is the ergot alkaloid bromocriptine (30). Results of different studies indicate that bromocriptine is a sympatholytic dopamine D_2 receptor agonist with 5-HT modulating activities (31). In a double-blind, placebo-controlled trial with 17 obese subjects, bromocriptine combined with a moderate hypocaloric diet reduced body weight to a greater extent than placebo. This effect is probably not only the result of appetite suppression, but also of an inhibition of lipogenesis. Bromocriptine also improved glucose tolerance in obese subjects (30). In ob/ob mice, bromocriptine administration in combination with the dopamine D_1 receptor agonist SKF 38393 was even more effective in reducing body weight, body fat, and food consumption, and in improving metabolic abnormalities like hyperglycemia, hyperinsulinemia, and hyperlipidemia (31, 98).

Doprexine (N-docosahexaenoyl, 3-hydroxytyramine / NMI 8739)

Doprexine is a conjugate of dopamine and the polyunsaturated fatty acid cis-docosahexaenoic acid. It crosses the blood-brain barrier much faster than dopamine and is presumed to act as a D_2presynaptic agonist (158). In mice and rats doprexine suppressed food intake, and in mice it did not induce tolerance over three weeks of administration (131). Dopamine and docosahexaenoic acid are natural brain constituents, and so far no serious side effects were observed in animal studies. Therefore, doprexine might be a safe and effective anti-obesity compound in humans (158).

Altogether, the dopaminergic drugs bromocriptine and doprexine may be useful for the therapy of obesity. Yet, clinical studies still have to prove that they are safe and effective without having an addictive potential.

Adrenergic and noradrenergic drugs

Noradrenalin acts in the paraventricular nucleus (PVN) of the hypothalamus on two different receptors with opposing functions (76). Whereas it inhibits feeding through α_1-receptors (76), activation of α_2-receptors enhances food intake (94). However, it is undisputed that different catecholaminergic agonists increase sympathetic activity and reduce appetite (29). The first adrenergic agents, amphetamines and closely related compounds like methamphetamine and benzphetamine, are no longer recommended for the treatment of obesity because of their substantial abuse potential (18, 110, 132). Diethylpropion, mazindol, and phentermine are the adrenergic drugs most commonly used by physicians in the United States to treat obesity (5). These three agents have appetite-suppressant activity and a minimal addiction or abuse potential (132). Adverse effects like insomnia, irritability, and nervousness were reported to be minor and were related to the central nervous system (56, 132). As mentioned previously, phentermine was used for some time in combination with fenfluramine, which is currently not on the market (26). Phenylpropanolamine is another adrenergic drug with weak appetite suppressant activity and a weak effect on energy expenditure (13). For further details about the adrenergic substances mentioned see (18, 29, 56, 59, 110, 132).

Ephedrine/caffeine

The sympathomimetic agent ephedrine suppresses food intake, probably via adrenergic pathways in the hypothalamus (1, 13), and produces a prolonged increase in resting energy expenditure (117). Ephedrine also stimulates noradrenalin secretion from peripheral nerve terminals. Caffeine inhibits noradrenalin degradation. Aspirin reduces the activity of prostaglandins that degrade noradrenalin after synaptic release and is sometimes added to the ephedrine/caffeine preparation. Therefore, the main effect of these three agents is to increase or prolong the noradrenalin action (5). The combination of ephedrine and caffeine can induce weight loss through an increase in energy expenditure and a decrease in food intake (116). Astrup et al. (1) calculated that 75% of weight loss is due to an anorectic effect and 25% to a thermogenic effect. In a placebo-controlled study they showed that chronic treat-

ment of obese patients with a diet and the ephedrine/caffeine combination reduced body weight compared to placebo. Either substance alone did not enhance the loss of body weight (1, 5). In addition, ephedrine plus caffeine prevented the decline in HDL cholesterol associated with weight loss (2). During the initial phase of treatment, adverse effects, like increased heart rate and blood pressure, increased serum insulin levels, tremor, insomnia, and dizziness can occur (1, 5). Ingerslev et al. (82), however, reported no blood pressure increasing effect of ephedrine/caffeine during short-term treatment in normotensive and hypertensive obese patients. According to a new study with rats, ephedrine and caffeine may mutually potentiate one another's amphetamine-like stimulating effect (166), but other results suggest limited reinforcing effects of this combination in rats (23).

If the patient tolerates the ephedrine/caffeine combination and heart rate and blood pressure are checked regularly, it appears to be a useful short-term adjunct to a weight-reducing diet. Nevertheless, few data on long-term administration exist and recently the FDA has expressed concerns about the safety of ephedrine because some fatalities have been associated with ephedrine-containing products (115).

β_3-*adrenoceptor agonists*

Energy expenditure comprises mainly the basal metabolic rate, the thermic effect of food, and the energy cost of physical activity (118). It is now generally accepted that there is a biological variability in daily energy expenditure in humans that is not a result of individual differences in body size, body composition, sex or age. A lower than normal metabolic rate or a reduced thermic effect of food may be a major risk factor for weight gain in humans (65, 118, 151). The idea to reduce body weight by increasing thermogenesis in various tissues like brown adipose tissue and skeletal muscle is not new. In fact, many naturally occurring substances such as thyroid hormones, insulin, growth hormone, androgens, 5-HT, and catecholamines increase thermogenesis. Different nutrients like potassium, magnesium, phosphate and zinc have also been reported to be thermogenic (1).

Catecholamines are major candidates for increasing thermogenesis. Unfortunately, they nonselectively stimulate α- and β-adrenoceptors and therefore increase heart rate and blood pressure. Catecholamines are also of limited use for obesity treatment because of their short half-life in plasma (86). Since it was demonstrated in animal models that brown adipose tissue thermogenesis and lipolysis in white adipocytes are associated with activation of an atypical β-adrenoceptor (=β_3-adrenoceptor), new antiobesity drugs were developed with selective β_3-action (43, 54, 86, 165). The increased thermogenesis can be explained by an augmented transcription of mRNA for the mitochondrial membrane uncoupling proteins (UCP-1-3) (165). UCPs are responsible for the exothermic transport of protons through the inner mitochondrial membrane, down their concentration gradient, and uncoupled from ATP synthesis (58, 119). The uncoupling proteins were originally assumed to be present only in brown adipose tissue (148). Whereas this is true for UCP-1, Gong et al. (58) demonstrated that UCP-2 and in particular the newly cloned UCP-3 are also expressed by other tissues such as muscle tissue and white adipose tissue. UCP expression is partly under the control of β_3-adrenergic stimulation. Treating rats with the β_3-adrenoceptor agonist (CL 316243) increased UCP mRNA levels in white adipose tissue (58). In adult humans skeletal muscle is quantitatively the major site of thermogenesis (28) and of UCP-3 expression. In rats, however, muscle UCP-3 is primarily under the control of thyroid hormones and is not effected by β_3-adrenergic stimulation (58). So far, the effect of β_3-adrenergic stimulation on skeletal muscle thermogenesis in humans has not been critically evaluated.

β_3-adrenoceptor agonists can also modulate metabolism independent of UCPs. For example, they stimulate free fatty acid (FFA) release from visceral fat depots (99), and enhance lipid (146, 159) and glucose oxidation (65), which could account for a feeding suppressive effect. Many new drugs with β_3-adrenoceptor agonist activity (BRL 26830A, BRL 35135, RO 40-2148, RO 16-8714, CL 316243, and ZD 7114) are now in clinical examination (29).

Most studies indicate that β_3-adrenoceptor agonists can increase resting energy expenditure by 10-20% and activate postprandial thermogenesis (2). On a 24 h basis, energy expenditure may be increased by 5-10% (2, 4). In a double-blind trial (18 weeks) with 40 obese subjects, weight loss was higher in the group receiving the β_3-adrenoceptor agonist BRL 26830A than in the placebo group (15 kg vs 10 kg). Both groups were prescribed a 3.35 MJ diet. (34).

In addition, administration of some β_3-agonists normalizes plasma insulin and glucose in rodents and diabetic patients (28, 43, 52, 53, 80) independent of the weight change (38, 165). This might be explained by the fact that β_3-adrenoceptor agonists activate the expression of the glucose-transporter four in adipose tissue and consequently increase glucose uptake in this tissue (38).

In general, β_3-adrenoceptor agonists cause no variations in heart rate and blood pressure (65). One reported side-effect is tremor, which is presumably due to nonspecific β_2-receptor stimulation in skeletal muscle (28, 34).

All in all, it is unlikely that β_3-adrenoceptor agonists are able to enormously increase energy expenditure in humans, because new data indicate that different to rodents, humans express β_3-adrenoceptors in brown, but not in white adipocytes (83), and adult humans have very little brown adipose tissue. Nevertheless, they might be useful in obesity therapy in combination with diet and exercise, because they appear to attenuate the decrease of resting metabolic rate during dieting. β_3-adrenoceptors also im-

prove insulin sensitivity (140) and may exert anabolic effects on skeletal muscle (119). More clinical studies with agonists that are selective for human β_3-adrenoceptor are needed, however, to evaluate if the results of rat studies are relevant for humans.

Histaminergic drugs

Several studies indicate that histaminergic neurons participate in the regulation of appetite (106, 145). Peripheral histamine can not cross the blood-brain barrier. Therefore, the synthesis of histamine from the amino acid histidine is the principle source of central nervous system histamine (157). Increased histidine transport into the brain leads to increased rates of histamine synthesis. Three different subtypes of brain histamine receptors (H_1, H_2 and H_3) are known (106). An elevated concentration of H_1 receptors was associated with a decrease in food intake (67). This is in line with other findings (92) showing that activation of brain H_1 receptors decreases food intake.

The activation of the H_3 receptor leads to a reduction of brain histamine synthesis and release, and, therefore, it has an opposite effect to the H_1 receptor activation. Consequently, intracerebroventricular infusion of an H_3 receptor antagonist increased the brain histamine level and depressed feeding in rats (106, 126). In rats, the new H_3 receptor antagonist GT-2016 crosses the blood-brain barrier and binds to cortical histamine H_3 receptors. GT-2016 increased histamine release by about 75% above baseline within 1 h (144). In studies with 24-h fasted rats and also in obese Zucker rats, GT-2016 significantly decreased food intake independent of the diet (145). This is, however, not in line with findings in obese Zucker rats, in which another H_3 receptor antagonist (thioperamide) failed to suppress food intake (126). The authors explained their results with a histamine receptor insensitivity in obese Zucker rats. However, they also demonstrated that the histaminergic system in the brain plays a crucial role in controlling food intake and energy balance (126). All in all, the H_1 and H_3 brain histamine receptors may be interesting future targets in obesity therapy.

Brain peptides

Corticotropin releasing factor (CRF)

Corticotropin releasing factor (CRF) is a neuropeptide that has long been known to reduce food intake when injected into the paraventricular nucleus of the hypothalamus (88, 97). The CRF-related peptide urocortin (156) is even more effective as an appetite suppressant than CRF itself (41). A reduced hypothalamic CRF level due to a dysregulation of the pituitary-adrenal axis may be associated with the development of obesity (41). However, CRF receptor agonists can not be used in the obesity treatment, because they trigger stress symptoms (71). The binding of CRF to its specific carrier protein (CRF binding protein, CRF-BP) in metabolic regulatory brain regions attenuates its ability to reduce food intake (41, 70). A new substance (CRF-BP ligand inhibitor), which dissociates CRF or urocortin from CRF-BP and increases endogenous brain levels of unbound CRF or urocortin, significantly attenuated weight gain after intracerebroventricular administration in obese Zucker rats (70). In contrast to CRF receptor agonists, it had no stimulating effect on adrenocorticotropic hormone secretion, heart rate or blood pressure (70, 71). Since CRF is considered to be one of the major central satiety substances, CRF-BP ligand inhibitors are potentially useful drugs in obesity treatment, although further studies are needed to establish their effectiveness and safety.

Neuropeptide Y

Neuropeptide Y (NPY) is another important neuropeptide that stimulates food intake when injected into the hypothalamus (17, 93, 95) and other brain areas. NPY belongs to a group of neuropeptides that also includes peptide YY (PYY) and pancreatic polypeptide (PP) (87, 137). It is synthesized by neurons of the arcuate nucleus and secreted from their terminals in the paraventricular nucleus and ventromedial hypothalamus (45, 96). NPY stimulates in particular carbohydrate intake (96). Besides inducing hyperphagia and hyperinsulinemia, NPY enhances liver and adipose tissue lipogenetic activity and increases basal corticosteronemia in rats. Interestingly, the same effects were observed when NPY-induced hyperphagia was prevented by pair-feeding (168). NPY receptors are found both in the central nervous system and in peripheral tissues. To date, six NPY receptor subtypes have been characterized (114) and four have been successfully cloned from rodent and human tissue (7, 138, 160). Some data (74, 87, 114) suggest that NPY stimulates eating through the Y_1 receptor. Yet, recent evidence indicates that the Y_5 receptor is the primary “feeding receptor” (51, 77, 128). This is in line with the selective down-regulation of Y_5 and not Y_1 receptors observed in obese Zucker rats (160). Another trial with mice lacking the NPY Y_5 receptor also demonstrated that the NPY Y_5 receptor does mediate some of the effects of centrally administered NPY (102). However, the NPY Y_5 receptor was not required for appropriate feeding under normal conditions or following food deprivation (102).

In addition, it is clear that neither a polymorphism in NPY Y_1 nor in NPY Y_5 receptor genes is responsible for the variability of body weight in humans (123). Findings that NPY knockout mice eat and gain weight normally suggest that NPY is not an obligatory part of the neuroendocrine network for the control of food intake and body weight (44). In addition, Hollopeter et al. (79) showed that NPY is not required for the development of obesity in diet-, chemical- and genetic-induced obesity of mice. Nevertheless, in the absence of NPY, ob/ob mice were

less obese and were less severely affected by diabetes and sterility (45). Therefore, NPY might contribute to forms of obesity associated with impaired leptin signaling (45).

Once the physiological role of the different NPY receptors is fully understood, it should be possible to develop selective NPY receptor antagonists as antiobesity drugs. However, presumably neither a NPY Y_1 nor a NPY Y_5 receptor antagonist will be a panacea in obesity therapy.

Ob-gene product leptin

The discovery of the ob gene product leptin in 1994 by Friedman and colleagues (167) resulted in enormous publicity, because leptin is considered to be the long sought lipostatic feedback signal in the control of body weight. In addition, the fact that administration of leptin to female mice triggered the onset of puberty and sexual maturity indicates that leptin controls reproductive functions (6, 26, 130).

Leptin is synthesized and secreted by white adipose tissue in proportion to the adipose mass (24, 50, 81) and, as shown recently, by the placenta of pregnant women (103). In rodents, the ob gene is also expressed in brown adipose tissue (125). Glucocorticoids and insulin are presumably involved in ob gene expression (125). Also, β_3-adrenoceptor stimulation seems to reduce leptin expression (139), whereas cytokines such as tumor necrosis factor-α and interleukin-1 stimulate leptin synthesis (15).

The CNS action of leptin on food intake and energy expenditure is mediated by different neuropetides. For example, leptin inhibited NPY gene expression in various brain regions including the arcuate nucleus (20, 25, 45, 109, 120, 136, 137) and increased CRF gene expression in the paraventricular nucleus (25, 147, 149). Recent studies identified further potential targets of leptin signaling in the hypothalamus. Central administration of leptin was associated with a decrease in hypothalamic galanin, melanin-concentrating hormone and proopiomelanocortin, and with an increase in neurotensin gene expression (124). Mizuno et al. (107), however, showed a stimulating effect of leptin on hypothalamic proopiomelanocortin neurons.

Although the exact mechanism of leptin action is not fully understood, it is clear that leptin reduces food intake and increases energy expenditure after peripheral and central administration in obese and lean laboratory animals (8, 25, 50, 54).

Most obese people, however, have high leptin plasma levels, and body fat content and plasma leptin concentration are highly correlated (50). This indicates that obesity in humans is not caused by a leptin deficiency (6). Yet, a higher proportion of total leptin circulates in the bound form in lean than in obese subjects (134). In addition, unlike marked changes in serum leptin, leptin concentration in the cerebrospinal fluid in obese humans is only modestly increased (134). This might be due to the fact that leptin crosses the blood-brain barrier through a saturable process (15, 134, 139). It is also interesting that independent from total body fat, leptin levels are higher in women than in men (15, 134). Presumably testosterone secretion suppresses serum leptin levels in men (113).

At the moment, the clinical relevance of leptin in obesity therapy can not be conclusively evaluated. Although obesity in humans is very rarely caused by leptin deficiency (6), a decreased sensitivity to leptin may contribute to the problem in some people (8, 25, 26, 50, 109, 129, 155). Sinha and Caro (134) assume that about 5% of the obese population are relatively leptin resistant and that they could benefit from leptin therapy. Still, so far no significant abnormality of the hypothalamic leptin receptor has been demonstrated in humans (15, 24, 134).

Short-term fasting or overfeeding (= negative or positive energy balance, respectively) triggers overproportional changes in plasma leptin level (37, 134). Therefore, leptin may function as a sensor of energy balance (134), and leptin administration during active weight loss might attenuate the compensatory neuroendocrine responses that may result in increased appetite in some patients with obesity. Leptin might therefore help them to reduce food consumption and to maintain their reduced weight after dieting (15, 130, 139).

Pancreatic lipase inhibitor

One new gastrointestinal lipase inhibitor is orlistat (tetrahydro-lipstatin/THL), a derivative of the naturally occurring lipase inhibitor lipstatin (68). Orlistat reacts with gastric, pancreatic, and pancreatic carboxylester lipases (29) to form a relatively stable orlistat-enzyme adduct. Consequently, triglyceride hydrolysis and the subsequent absorption of free fatty acids and monoglycerides is reduced (61), and fecal fat excretion is increased (68). Orlistat reacts specifically with lipase and has no effect on the activity of other hydrolases like amylase, trypsin, and pancreatic phospholipase A_2 (61). However, the inhibition of the pancreatic carboxyester lipase leads to a reduced hydrolysis and absorption of lipid-soluble vitamins (29).

In human volunteers, administration of 120 mg orlistat three times a day (tid) caused an excretion of about 30% of ingested fat and a caloric deficit of about 200 calories per day (61). In different parallel-group, placebo-controlled studies with treatment periods in the range of 6 to 24 months, patients receiving orlistat lost more body weight (85, 135, 152) and were more successful in maintaining the weight loss than control subjects, which only received a calorie-restricted diet (85, 135). Moreover, orlistat decreased plasma total cholesterol and LDL cholesterol to a greater extent than expected from weight loss alone (135). Orlistat-treated patients with type 2 diabetes achieved greater weight loss, improved glycemic control,

and the dose of oral hypoglycemic medication could be decrease more than in the placebo group (78)

Nevertheless, patients reported side-effects such as abdominal pain, diarrhea, flatulence, looseness of stools or occasional anal leakage (29, 85). Generally, the tolerability of orlistat was related to the amount of fat in the diet. With a diet containing high amounts of fat, less of the lipase inhibitor was tolerated compared with a low fat diet (68). Furthermore, orlistat decreased mean plasma concentrations of the fat-soluble vitamins, D and E, and β-carotene, although vitamin levels of most patients remained within the clinical reference range (85, 135, 152).

Most of the administered drug (83%) is excreted as an intact molecule with the feces, and only a small percentage is absorbed (1.5-4%) (61). This is confirmed by Sjöström et al. (135) showing that even after a 24 months treatment period with orlistat, plasma concentrations of orlistat were measurable, but very low, with no evidence of accumulation. Therefore, the potential for a hazardous effect on postabsorptive metabolism should be low (61). The finding that breast neoplasms were diagnosed in 11 female patients receiving orlistat (120 mg tid, compared with 3 cases in the placebo group, however, caused doubt concerning the safety of orlistat (29, 104). After evaluating the size of the tumors and length of time that the female patients were on orlistat, it was concluded that 8 of the 11 tumors were present prior the beginning of the medication and consequently could not be caused by the therapy. Thus, there was no difference in the incidence of breast cancer between the orlistat and the placebo group (104, 108). In May 1998, the FDA issued a letter of approvability for orlistat and if certain conditions such as submission of follow-up safety data are fulfilled, orlistat will achieve final approval (121). Recently, orlistat has also received approval from the European Commission (122).

Overall, orlistat in conjunction with a mildly energy-restricted diet causes an additional caloric deficit due to a reduction in fat absorption and is, therefore, a useful adjunct for obesity therapy. Without dieting, the prescription of orlistat makes no sense, because patients are likely to eat more food to compensate for the caloric deficit. Plasma concentrations of fat-soluble vitamins, however, should be controlled regularly, and if necessary, the vitamins should be supplemented.

It is of course also possible to use fat substitutes in an attempt to reduce fat absorption. One of the most important fat substitutes is olestra, a mixture of hexa-, hepta-, and octa-esters of sucrose with long-chain fatty acids. For further details about fat substitutes see Cerulli et al. (29) and Menden (105).

Other potential targets for the treatment of obesity

The α-melanocyte stimulating hormone (α-MSH), a product of the proopiomelanocortin gene, inhibits eating by acting through the melanocortin-4 (MC4) receptor (107, 142). Therefore, a MC4 receptor agonist might be a useful antiobesity agent (142).

As mentioned previously, UCP-2 and 3 are expressed by white adipose tissue and skeletal muscle (142), and, as shown recently, UCP-2 mRNA is decreased in skeletal muscle (111) and in intraperitoneal adipose tissue of obese humans (112). Therefore, activators of these proteins other than β_3-adrenoceptor agonists might also be interesting for obesity therapy (26).

Further potential neuropeptide targets for appetite suppressants include receptors for melanocyte concentrating hormone (MCH), galanin, and opiod peptides (26). Of the gastrointestinal peptides implicated in the control of food intake, GLP-1 might be the most interesting for the development of antiobesity agents.

Final remarks

In most adults, body weight and body fat remain relatively constant over many years despite large variations of energy intake and expenditure. A very complex set of peripheral (hormones, metabolites, fuel oxidation) and central (neuropeptides and neurotransmitters) signals controls food intake. Therefore, it is unlikely that one signal substance can overwhelm all the other control mechanisms. A panacea for weight loss might never be found and probably does not exist (164). Consequently, most antiobesity drugs so far cause only a modest weight loss and tend to lose their effectiveness with long-term administration. In addition, after discontinuation of antiobesity drugs, body weight generally returns to pre-treatment level. Therefore, chronic treatment is required to help patients to maintain their reduced body weight (57).

In this context, it is important to consider that every antiobesity drug has side-effects and, as demonstrated for dexfenfluramine, these undesirable effects are not always immediately obvious and might put people at risk (75). Therefore, the prescription of antiobesity drugs should be restricted to people who have an augmented health risk as a result of their excessively high body weight. In addition, drugs should only be used as an adjunct to diet and exercise to help patients to maintain their voluntary change in eating behavior (101).

Given the complex interactions and redundancies in the physiological control of energy balance, a parallel intervention in multiple regulatory pathways may be the most promising approach to avoid compensation as a consequence of the manipulation of one single pathway in control of body weight (109). While such an approach reduces the likelihood of compensation, it may increase the risk of side-effects (75). Finally, further research is needed to understand the genetic (16, 20) and physiological basis of obesity. In the future that knowledge might help to develop even more specific pharmacological agents that can more efficiently control body weight with fewer hazards.

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