Recent Advances in Obesity Pharmacotherapy

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Abstract: Obesity is considered a worldwide epidemic. Weight reduction by means of lifestyle changes is difficult to achieve, and pharmacotherapy is frequently needed. Although all currently approved anti-obesity agents have proven to be effective to achieve some degree of weight reduction and improve cardiometabolic risk factors, different compounds differ in their mechanism of action and safety profile. However, it is still difficult to achieve and maintain therapeutic objectives along time. The aim of the present article is to summarize the main characteristics of available anti-obesity agents and to explore novel agents that may provide significant clinical benefits in the future.

Key Words: Anti-obesity agents, obesity, pharmacotherapy, sibutramine, orlistat, rimonabant.

INTRODUCTION

The term epidemic is frequently used to describe the rapidly increasing rate of obesity worldwide, currently affecting over 1.1 billion individuals around the globe [1]. According to the National Health and Nutrition Examination Survey, 2003 to 2004, prevalence of obesity in the United States is 31.1% and 33.2% in men and women, respectively, with particularly high rates among non-Hispanic black Americans and Mexican Americans [2].

Obesity should not be considered as a cosmetic or body-image issue but rather as a chronic disease [1]. It is associated with multiple coexisting conditions (such as hypertension, glucose intolerance, dyslipidemia, and obstructive sleep apnea), and an increased risk of death from cardiovascular disease, diabetes, kidney disease, and obesity-related cancers (colon, breast, esophageal, uterine, ovarian, kidney, and pancreatic) [3, 4].

Although there are no randomized controlled trials which clearly establish the effects of weight loss on overweight and obese patients mortality rates, present data confirm that losing even as little as five to ten percent of initial body weight is associated with an improvement in cardiovascular risk factors [5-7]. However, the lack of large randomized controlled trials demonstrating that the chronic use of antiobesity drugs can reduce the incidence of weight-associated complications (especially major cardiovascular events) and prolong life expectancy while preserving quality of life is a major limitation that needs to be overcome. Nevertheless, this evidence is also missing for lifestyle interventions, essentially because of poor long-term compliance [8].

According to the National Institute of Health (NIH) Guidelines, initial anti-obesity therapy should be based on a combination of diet modification, increased physical activity, and behavior therapy [9]. However, considering that a great amount of patients fail to accomplish goal treatments, anti-obesity agents are frequently used as an adjunct for lifestyle changes. Eligible patients for pharmacotherapy include patients with a body mass index (BMI) greater than or equal to 30 kg/m^2 or a BMI of 27-30 kg/m^2 with one or more obesity-related disorders [9], especially those who do not achieve a substantial weight loss after 6 months of lifestyle changes.

In the year 2008, there are three main anti-obesity drugs used for chronic treatment of obesity: Orlistat and sibutramine (approved for long term use in most of the countries), and rimonabant (approved for the treatment of obesity in most of Europe and in Mexico and Argentina, but not by the US Food and Drug Administration (FDA) because of concerns about adverse Effects) [4]. The aim of the present article is to revise the main characteristics of these drugs, and to provide information regarding new anti-obesity compounds under development.

ORLISTAT

Pharmacology

If we think of obesity as an imbalance between energy intake and energy expenditure, it seems logical to assume that one pharmacological agent is directed to reduce energy intake by means of reducing fat absorption. Orlistat, a selective and potent inhibitor of gastrointestinal lipases involved in triglyceride hydrolysis, restricts the absorption of triglycerides from the gastrointestinal tract [10, 11]. It has been demonstrated that it reduces fat absorption in a dose-dependent fashion, with a maximal inhibition of 30% fat absorption at a dosage of 120 mg 3 times a day [11]. Because of low systemic absorption and first-pass metabolism, the bioavailability of orlistat is less than 1%, and most of the drug is excreted unchanged in feces [12, 13].

As is expected as a result of its mechanism of action, major adverse effects are gastrointestinal, and systemic adverse effects are minimal because of the lack of systemic

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Table 1. Drugs Currently Approved for Chronic Treatment of Obesity

	Sibutramine	Orlistat	Rimonabant
Mechanism of action	Inhibits noradrenaline and serotonin reuptake	Inhibits gastrointestinal lipases. Reduces fat absorption in 30%	Antagonist of CB1 endocannabinoid receptors
Metabolism	Hepatic (cytochrome P450 3A4 to active metabolites)	Partial metabolism to inactive metabolites	Hepatic (cytochrome P450 3A4 to inactive metabolites)
Elimination	Mainly urinary	Fecal	Fecal
Weight reduction (compared to placebo)	Approximately 4.2 kg more than placebo	Approximately 2.7 kg more than placebo	Approximately 4.7 to 5.4 kg more than placebo
Main adverse effects	Insomnia, nausea, dry mouth, constipation, headache, moderate increases in blood pressure and heart rate	Fatty stools, fecal incontinence	Nausea, dizziness, diarrhea, insomnia, depression and mood disorders
Interactions	Monoamino oxidase inhibitors or serotoninergic drugs	Liposoluble vitamins Reduces amiodarone and cyclosporine absorption. Might potentiate warfarin effects	ketoconazol, ritonavir, claritromicine
Contraindications	Uncontrolled hypertension, cardiovascular disease, tachycardia	Diarrhea	Breast feeding. Hypersensitivity. Depression or under antidepressive medication

absorption [13]. Frequent gastrointestinal adverse effects include fatty/oily stools, fecal urgency, diarrhea, flatulence, abdominal pain, and fecal spotting [14]. However, it is important to mention that complaints of mild to moderately severe gastrointestinal adverse effects generally decrease in frequency with ongoing orlistat treatment [15].

Considering fecal spotting, it has been reported that this adverse effect occurs when patients with subclinical anorectal dysfunction are exposed to the effects of orlistat on the stool, but would not be related to a direct effect of orlistat on anorectal function [16].

Another important issue related to orlistat safety profile is its possible interaction with fat-soluble vitamins and drugs. The absorption of fat-soluble vitamins may be decreased by orlistat [14]. This effect was observed in the XENDOS (Xenical in the Prevention of Diabetes in Obese Subjects) study [17], where plasma concentrations for all assessed fat soluble vitamins, with the exception of 1,25 hydroxyvitamin D, were significantly decreased in the orlistat group compared with the placebo group after 4 years of treatment. However, the mean level of each assessed vitamin remained within its reference range during the 4-years of treatment with orlistat.

This effect on fat-soluble vitamin absorption might explain its possible interaction with warfarin, as a reduction in vitamin K absorption could result in a lowering of warfarin dose requirements [18]. Consequently, patients stabilized on warfarin should be closely monitored for changes in coagulation parameters [14]. Other possible interactions might occur with amiodarone [19], ciclosporin [20] and highly lipophylic drugs, such as antiepileptic drugs [21], and there is evidence that the combination of orlistat with antidiabetic drugs causes increased episodes of mild to moderate hypoglycaemia compared with placebo in diabetic patients [22].

Efficacy

According to a recent Cochrane meta-analysis, orlistat treatment induces greater reductions in body weight compared to placebo [23]. In this study, when weight loss was expressed as absolute number of kilograms lost, orlistat showed a 2.7 kg greater weight loss compared to placebo, and, expressed as percentage, a 2.9% greater weight loss in orlistat treated patients compared to placebo. Interestingly, a greater number of participants in the orlistat group achieved five percent and ten percent weight loss compared to placebo (21% more participants in the orlistat group achieved five percent weight loss, and 12% achieved ten percent weight loss compared to placebo).

The XENDOS study demonstrated that orlistat treatment can reduce the progression to diabetes in comparison with lifestyle changes alone (relative risk reduction of 37%), especially in obese patients with impaired glucose tolerance [17]. This finding has been supported by another randomized controlled trial which showed that the incidence of new type-2 diabetes was significantly decreased in patients using orlistat for weight maintenance after initial weight loss [24].

Orlistat also induces a decrease in blood pressure by 1.8 mm Hg systolic and 1.6 mm Hg diastolic, LDL cholesterol by 0.27 mmol/L, and fasting glucose in patients with diabetes by 0.8 mmol/L. No clinically significant effects on triglycerides or HDL cholesterol were seen [23].

There is also data supporting that orlistat would be useful in the treatment of non alcoholic fatty liver, as it has been shown to improve alanine transferase (ALT) levels and steatosis in these patients [25].

SIBUTRAMINE

Pharmacology

Sibutramine is a selective inhibitor of the reuptake of monoamines, primarily serotonin and noradrenaline and, to a lesser extent, dopamine [26], originally developed as an antidepressant [27]. It is capable of reducing food intake by means of increasing satiety, and also attenuates the fall in metabolic rate which occurs during weight loss [28], probably by stimulating thermogenesis [29] (although this secondary action is supposed to play a minor part in weight reduction).

Sibutramine undergoes extensive first-pass metabolism, mainly by hepatic cytochrome P450 3A4 enzymes, to two active metabolites, which are more potent than the parent compound [30]. Most of the drug and its active metabolites are renally excreted [13].

Sibutramine is overall a safe and well-tolerated agent. Frequent side effects include insomnia, dry mouth, constipation, nausea and headache. However, sibutramine has been associated with increases in blood pressure (BP) and pulse rate, raising concerns about a potential increase in cardiac risk [31].

Taking into account its mechanism of action, it is comprehensible that one of its adverse effects could be an increase in blood pressure and heart rate, due to inhibition of peripheral noradrenaline uptake. It has been reported that sibutramine can increase systolic and diastolic blood pressure in 2-3 and 1-2 mmHg, respectively, and raise heart rate in 4-5 beats per minute [32, 33]. This has lead the Italian regulatory authorities to suspend its approval in the year 2002 after the appearance of a publication from the British health authorities that suspected an association between sibutramine and two cases of cardiovascular death and 212 reports of adverse reactions in patients treated with this drug [34]. However, this temporal contraindication was only preventive and was not a consequence of an specific study of the adverse consequences / benefits ratio of the use of this compound.

In order to determine if sibutramine has any effect on cardiovascular morbity and mortality, the ongoing SCOUT (Sibutramine Cardiovascular Morbidity/Mortality Outcomes Trial) trial pretends to evaluate the effects of the treatment with sibutramine or placebo associated to lifestyle changes, on the incidence of cardiovascular mortality and cardiovascular events in a population of obese with high cardiovascular risk [35]. According to a report from an initial stage of this study, of 6 weeks of duration, in which sibutramine safety profile was evaluated, the authors suggest that this agent could have a beneficial effect in high cardiovascular risk patients [35]. As a matter of fact, meanwhile the authors expected that 25% percent of patients included in the initial stage of SCOUT discontinue the treatment due to the appearance of adverse events related to the drug, only 732 patients (6.8%) did not complete the 6 week evaluation period, and cardiac disorders (0.6%) and blood pressure increase (0.2%) caused a minority of discontinuations. Clearly, these results were lesser than those expected based on the high cardiovascular risk of the study population, and lead the authors to propose that sibutramine might be useful in high cardiovascular risk patients. However, it is important to consider that this data come from an initial stage of the study and only takes into account the short term effects of the drug. Accordingly, it is important to wait until the end of this trial in order to confirm this opinion from the authors.

Another interesting aspect of this initial report is related to the effects of sibutramine on blood pressure. According to a sub-analysis, the SCOUT researchers found in patients that achieved a reduction of more than 5% of their initial weight, that systolic/ diastolic blood pressure diminished -7.5/ -2.5 mmHg in hypertensive patients and -2.0/ 0.25 mmHg in normotensive patients. On the other hand, in patients that only achieved a reduction of less that 5% of their initial weight, sibutramine only reduced blood pressure in hypertensive patients (-4.5/ -1.5 mmHg) but it was associated with an increase in blood pressure (1.5/ 1.5 mmHg) in normotensive patients. These results would indicate that sibutramine effects on blood pressure depend on previous values of blood pressure and the magnitude of the weight reduction achieved. However, it is important to mention that in another important trial (the STORM study), two years of treatment with sibutramine were associated with an increase in blood pressure and heart rate [36].

Efficacy

Mean weight reduction with sibutramine is 4.2 kg higher than with placebo [37]. According to studies in diabetic patients, sibutramine improves insulin sensitivity, reduces total cholesterol (> 12%), LDL cholesterol (18%), triglycerides (15%) and ApoB (13%) levels, and increases HDL cholesterol values in more than 1%. It is important to mention that changes in HDL cholesterol and triglycerides levels exceed those atribuited to weight reduction alone [38]. It has been described that sibutramine reduces uric acid levels, C reactive protein, resistin and leptin levels, and increases adiponectin levels [38].

RIMONABANT

Pharmacology

Rimonabant is a selective antagonist of the cannabinoid type 1 receptor which has been shown to be involved in the central and peripheral regulation of food intake and the central nervous system rewarding system [39]. The drug is hepatically metabolized and excreted in bile and, because of a larger peripheral volume of distribution, obese individuals have a drug half-life that is twice as long (16 days) as non-obese people [13].

The most frequent adverse events are nausea, dizziness, diarrhea, and insomnia, each occurring 1−9% more frequently than with placebo [13].

Although rimonabant is generally well tolerated [40], its use has been associated with increases in depressed mood and depression. According to a recent meta-analyisis, patients receiving rimonabant are 2-5 times more likely to discontinue the treatment because of depressive mood disorders than those given placebo, and 3 times more likely to discontinue because of anxiety [41]. At this point it is interesting to mention that in the recent STRADIVARIUS (Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant –The Intravascular Ultrasound Study) trial, the rate of psychiatric adverse effects, primarily depression and anxiety, among patients randomized to receive rimonabant was alarmingly high (43.4% *vs*. 28.4% in the placebo group) [42]. In fact, more than 1 in 7 patients developed psychiatric adverse effects attributable to the drug. This might be related to the fact that the STRADIVARIUS study did not exclude patients with prior psychiatric disorders [43], what results in a less selected study population than in other studies.

Of concern, an analysis by the FDA of all randomized clinical trials evaluating rimonabant, including trials focused on smoking cessation, suggested that a 20-mg dose was associated with a 2-fold higher suicide risk [44].

Efficacy

Rimonabant´s efficacy has been tested in different populations during the RIO (Rimonabant In Obesity) program. This program comprised three large placebo-controlled trials in overweight ⁄ obese non-diabetic patients, comparing rimonabant 5 mg and 20 mg with placebo: two 2-year (RIO Europe and RIO North America) [40, 45, 46] and one 1-year trials (RIO-Lipids) in patients with untreated dyslipidaemia [47, 48]; and one trial (The RIO Diabetes trial) that investigated the efficacy and safety of rimonabant in overweight ⁄ obese patients with type-2 diabetes [49].

Regarding rimonabant´s efficacy in overweight / obese non-diabetic patients, rimonabant induced a significant weight loss (-4.7 to -5.4 kg) greater than placebo and a reduction in waist circumference of 3.6 to 4.7 cm [40, 46] after one year of treatment, and these changes persisted during the second year of pharmacotherapy [45, 46].

It was also associated with reductions in triglyceride levels (-12.4 to -15.1%), and increases in HDL cholesterol levels (+7.2 to +8.9%) [40, 45, 46].

Confirming data of metabolic parameters, the RIO lipid trial also found an improvement in lipid profile with rimonabant treatment [47], that could be attributed to a significant increase in plasma adiponectin levels [47, 48], and a diminishment in C-reactive protein levels. Interestingly, although LDL cholesterol levels were not affected by rimonabant, it was associated with a shift to a lower proportion of small-dense LDL particles [47].

Fasting plasma insulin concentrations and HOMA (Homeostasis Model Assessment) insulin resistance index were significantly decreased in patients receiving rimonabant 20 mg compared with placebo, and the prevalence of metabolic syndrome was significantly reduced in all three RIO trials performed in non-diabetic individuals [48].

According to the analysis of pooled data from RIO study results, rimonabant induces a moderate reduction in systolic and diastolic blood pressure related to weight loss, which is greater in patients with elevated blood pressure at baseline [50]. However, it is important to mention that in the whole population sample the blood pressure reduction was related significantly to body weight loss, which appears to be the major determinant of the effects of the drug on blood pressure [51].

In obese type-2 diabetic patients under treatment with metformin or sulphonylurea, the RIO Diabetes study found that treatment with rimonabant enabled a greater number of patients to attain the HbA1c American Diabetes Association target (HbA1c < 7%: 67.9% versus 47.6% with placebo) and the HbA1c International Diabetes Federation target (HbA1c < 6.5%: 42.9% versus 20.8% with placebo). In patients with higher HbA1c levels (≥ 8%) at baseline, greater reductions of 0.3% and 1.1% were observed in the placebo and rimonabant 20 mg treatment groups, respectively [49]. Similar results were observed in the SERENADE study (a 6 month trial in overweight / obese patients with recent onset diabetes treated with diet alone) [52], confirming the beneficial effects of this compound in diabetic patients.

The RIO Diabetes study also reported a reduction in liver enzymes (especially alanine transferase – ALT) in rimonabant treated patients, in addition to improving cardiometabolic risk factors in overweight / obese patients with type 2 diabetes [48, 49].

Recently, the STRADIVARIUS trial explored the effects of rimonabant treatment on progression of coronary atherosclerosis over 18 months in patients with coronary artery disease and abdominal obesity [42]. Disappointingly, although patients assigned to receive rimonabant had greater weight loss and improvements in metabolic profile, no significant differences were observed between the 2 groups in the primary efficacy end point, change in percent atheroma volume. However, rimonabant had a favorable effect on the secondary end point, change in total atheroma volume [42], suggesting that the strategy of using this drug to reduce progression of coronary artery disease may be useful but will require further study to confirm an antiatherosclerotic effect.

NEW ANTI-OBESITY AGENTS

Considering the relatively low weight loss efficacy and the adverse effect profile of approved anti-obesity agents [13, 23, 37, 38], a high interest exists in developing new pharmacological agents for weight reduction. In the last years, considerable progress has been made in the elucidation of molecular and humoral mechanisms involved in the pathophysiology of obesity and regulation of energy balance. Identification of new molecular targets allows the design of investigational anti-obesity agents with different mechanisms of action than approved drugs, and opens the possibility of associating them with current anti-obesity agents to achieve greater weight loss efficacy.

Several new chemical entities are under investigation in different stages of preclinical and clinical development. Some new anti-obesity drugs are designed to overcome limitations of drugs on the market. For instance, taranabant is a new CB-1 receptor inverse agonist under clinical development for weight reduction that is structurally different from rimonabant [53]. In animal models of obesity, taranabant inhibited in a dose-dependent fashion food intake and weight gain leading to weight loss and decrease in fat mass after

Table 2. Investigational Anti-Obesity Drugs

Drug Under Development	Molecular Mechanism of Action	Weight Loss Mechanism
Exenatide	GLP-1 analog	Increase saciety
Pramlintide	Amylin analog	Effects on eating behavior
CNTFAx15	CNTF analog	Reduction of feeding
Cetilistat	inhibitor of gastrointestinal lipase	Reduction of fat absorption
taranabant	CB-1 receptor inverse agonist	Reduction of feeding
Locarsetin	5-HT2C agonist	Supression of appetitive
Atomoxetine	NA uptake inhibitor	Supression of appetitive
GSK-858464, AMG-076, NGD-4715	MCH-1 receptor antagonists	Reduced food intake
Intranasal leptin	Leptin receptor agonism	Anorexigenic actions
MK-0557	NPY5 receptor antagonist	Anorexigenic actions
N-5984	β3-adrenoceptor agonism	Lipolisis
AOD 9604	Human growth hormone fragment	Increases energy expenditure and fat oxidation
Oleoyl-estrone		Decrease in food intake

Abbreviations: GLP-1: glucagon-like peptide-1, DGAT-1: Acyl-CoA:diacylglycerol-acyltranferase-1, CNTF: Ciliary neurotrophic factor.

chronic treatment [53]. This study also demonstrated that the magnitude of weight loss is highly correlated with brain CB-1 receptors occupancy, showing that only partial CB1 receptors occupancy (30%-40%) is needed to induce weight reduction. More recently, a single oral dose study of taranabant in healthy volunteers have demonstrated that taranabant shows a pharmacokinetic profile suitable for a once-daily dosing regimen [54]. Additionally, the authors found that adverse events associated with single doses of taranabant were generally mild and transient [54].

Considering that CB-1 receptor inverse agonists exert their weight loss actions on the central nervous system and in the periphery [55], an attractive approach is the design of CB-1 receptor inverse agonists that are not capable to diffuse through the blood brain barrier. Although theoretically these agents would be free of adverse effects at the central nervous system, they probably suffer form a reduced efficacy as appetite suppressants [55].

New drugs acting at central serotoninergic neurotransmission have been developed with the aim of reducing cardiovascular adverse effects of 5-HT reuptake inhibitors [56, 57]. A detailed screening of sibutramine appetitive suppression action shows that this drug directly activates hypothalamic POMC neurons through activation of 5-HT2C receptors. Therefore, in the last years new selective 5-HT2C agonists have been designed. For instance, lorcaserin is highly selective for human 5-HT2C over other human 5-HT receptors. Morevover, this new chemical entity does not compete for binding of ligands to serotonin, dopamine, and norepinephrine transporters, and it does not alter their function *in vitro* [56]. Pharmacokinetic propierties of locarsetin have also been evaluated in an experimental model of obesity showing a high bioavailability and a plasma half-life of approximately 4 hours after oral administration. After 28 days of oral administration (36 mg/kg b.i.d.), locarsetin promotes an 8.5% decrease in weight gain. Considering these results, lorcaserin was selected for further evaluation in clinical trials for the treatment of obesity [57].

Atomoxetine is another potential anti-obesity drug that acts by inhibition of noradrenaline uptake [58]. Although this drug is actually indicated for the treatment of attention-deficit/hyperactivity disorder, a 12/week randomized placebo-controlled study have demonstrated that atomoxetine reduce body weight in 3.7% with regard to placebo treatment. In this study, atomoxetine was well tolerated with minimal side events [58]. Atomoxetine seems also to be effective and well tolerated in the treatment of obesity associated to binge-eating disorder.

Ciliary neurotrophic factor (CNTF), a glial cell-produced cytokine, was firstly introduced in the market for the treatment of neurodegenerative disorders. In clinical trials for neurodegenerative diseases, CNTF reduced body weight by 10-15% [59]. Although the exact mechanism of weight reduction induced by CNTF is unknown, systemic administration of this cytokine activates genes in the arcuate nuclei inducing anorexogenic neuronal signaling [60]. In addition, administration of CNTF in leptin resistance models of obesity resulted in reduced feeding and body weight [60]. CNTF also exerts peripheral actions by upregulating AMPK activation, and increasing thereby fatty acid oxidation. Other beneficial effects of CNTF are the decrease of liver steatosis and the improvement of lipid induced insulin resistance [61]. A human recombinant variant of CNTF, CNTFAx15, has been studied in a phase II clinical trial in subjects with a median BMI of ~41 [62]. Although CNTFAx15 induced a weight loss of 3–4 kg after 84 days, patients administered high doses experienced nausea, and numerous subjects developed neutralizing anti-CNTFAx15 antibodies [62]. In addition, a follow-up study showed that patients treated with CNTFAx15 regained body weight [62].

Novel inhibitors of gastrointestinal lipases are also under clinical development with the aim to reduce frecuency of adverse effects of this therapeutic group. Actually, cetilistat (ATL-962) is under Phase III evaluation, and results show that this drug may offer a better tolerability in comparison with orlistat [63]. In a 12-week randomized, placebo-controlled study of weight reduction in obese patients, it was found that cetilistat was well tolerated with a frequency of withdrawal owing to treatment-emergent adverse events similar to placebo. Although the incidence of gastrointestinal adverse events was increased in the cetilistat-treated groups with regard to placebo, adverse events, like flatus with discharge and oily spotting, occurred only in 1.8-2.8% of subjects treated with the new lipase inhibitor [64]. Regarding body weight loss efficacy, 12-week treatment with cetilistat reduced mean body weight to similar extents at all doses, which were statistically significant compared to placebo (60 mg t.i.d. 3.3 kg, P<0.03; 120 mg t.i.d. 3.5 kg, P=0.02; 240 mg t.i.d. 4.1 kg, P<0.001). In addition, cetilistat also slightly diminished total cholesterol and LDL-C levels. The good risk benefit profile of cetilistat promotes further evaluation for the pharmacotherapy of obesity and related disorders [64].

Recently, pramlintide, an analog of amylin have been approved for the treatment of diabetes in association with insulin. Amylin is a beta-cell-derived neurohormone that exerts multiple effects on eating behavior, including reductions in meal size, intake of highly palatable foods, and stress-induced sucrose consumption [65]. Therefore, pramlintide may be an attractive therapeutic strategy for the treatment of obesity in type 2 diabetes patients. Smith *et al.* [66] evaluated the effect of pramlintide on caloric intake, meal sizes and control of eating in obese subjects during 6 weeks. In this study, pramlintide treatment elicited significant mean reductions from baseline in body weight on day 44 (-2.1 +/- 0.3 *vs*. +0.1 +/- 0.4%, P < 0.001) due to a reduced 24-h caloric intake, suggesting a potential role of pramlintide in the treatment of obesity.

Recently, incretin mimetic drugs have been introduced in the pharmacological therapy of diabetes [65]. These drugs act by enhancing stimulation of glucagon-like peptide-1 (GLP-1) and are associated with an improvement of glucose control and weight loss [65]. Exenatide, an analog of GLP-1, also improves lipid parameters, blood pressure, and C-reactive protein levels [67]. GLP-1 causes satiation leading to meal termination and bodyweight reduction. Viswanathan *et al.* [68] showed in a retrospective analysis of 52 patients treated with exenatide that mean body weight decreased by 6.46 kg in patients treated with exenatide and increased by 2.4 kg in patients that have discontinued the drug (P<001). Therefore, exenatide seems to be an attractive approach for the treatment of obesity in type 2 diabetes patients.

Nevertheless, more interest appears in the design and evaluation of new chemical entities acting on novel molecular and humoral mechanisms that participate in the pathophysiology of obesity [55]. For instance, melanin-concentrating hormone (MCH) is produced by hypothalamic neurons acting as an endogenous orexigenic agent at the MCH-1 receptor subtype [69]. Nowadays, three MCH-1 receptor antagonists are under clinical development, GSK-858464, AMG-076, NGD-4715 [69]. Preclinical evidence indicates that MCH-1 antagonism may be a promising therapeutic approach for treatment of obesity, considering that these novel agents promote a decrease of bodyweight and adiposity principally due to reduced food intake [69]. Although bodyweight loss is sustained with continuous drug administration, hypophagic effect of MCH-1 receptor antagonists declines with time. Some studies found that the caloric intake in MCH-1 antagonist treated animals returns to that of control animals [69]. More recently, it was found that MCH-1 receptor regulates deep slow-wave sleep-REM sleep cycle and antagonist of this receptor significantly decrease deep sleep without recovery interfering with sleep dependent memory consolidation [70]. Therefore, the clinical impact of sleep disturbance promoted by MCH-1 receptor antagonists must be weight out to in clinical studies.

Nowadays, knowledge regarding central regulation of energy balance is increasing enormously. One of the most relevant discoveries was the identification of leptin as a pivotal regulator of the adipose tissue – central axis. Leptin is expressed in adipocytes and informs the central nervous system about status of energy reserves. Circulating levels of leptin are highly related to the number and size of adipocytes [55]. Leptin acts on the arcuate nucleus activating specific receptors on two different neuronal systems. Leptin stimulates neurons expressing pro-opiomelanocortin (POMC), a precursor of alpha-melanocyte-stimulating hormone (α-MSH), and cocaine and amphetamine-related transcript (CART). α-MSH stimulates melanocortin-4 (MC-4) receptors in the paraventricular nucleus reducing thereby the appetite. CART also exerts anorexigenic actions. On the other hand, leptin inhibits neurons expressing neuropeptide Y (NPY) and Agouti-related protein (AgRP). Whilst NPY shows orexigenic actions by activation of NPY-1 and NPY-5 receptors, AgRP is an endogenous inverse agonist at MC-3 and MC-4 receptors [55].

Considering the molecular insights of leptin central action, several pharmacological targets can be identified theoretically for the design of new anti-obesity agents. However, pharmacological strategies aimed at increasing leptin action have some limitations.

Despite the pivotal role of leptin in bodyweight regulation, nowadays no agonists of leptin receptors are under development. Administration of leptin in obese patients has shown disappointing results because of the existence of leptin resistance in a high proportion of these patients [71]. However, recently it was discovered that insensitivity to leptin in obese patients is probably partially a consequence of an impaired transport of leptin across the blood-brain barrier by a saturable mechanism [72]. The nose provides an effective way for central delivering of leptin, bypassing the blood-brain barrier and avoiding systemic side effects [73]. Intra-nasal delivery of leptin overcomes this leptin resistance leading to weight loss [74]. It was found that intranasal leptin delivery in rats resulted in supraphysiological brain levels, especially in the hypothalamus [75].

Acting at pathways downstream of leptin is also an interesting pharmacological strategy to overcome leptin resistance [55]. In this way, antagonists of NPY receptor might have anti-obesity efficacy. However, NPY seems to have a limited role in central leptin actions, considering that knockout mice, not expressing NPY Y1 and NPY Y5 receptors, did not result in a complete bodyweight reduction to a lean phenotype [76, 77].

More recently, it was found that MK-0557, a NPY5 receptor antagonist, did not significantly increase the weight loss efficacy of either orlistat or sibutramine monotherapy [78]. In another study, MK-0557 was evaluated in a 1-yr clinical trial achieving only modest weight loss. These studies clearly demonstrate that selective NPY5 receptor antagonism exerts limited anti-obesity efficacy. Therefore, dual NPY1 and NPY5 antagonist are currently under development with aim at increasing therapeutic efficacy of this pharmacological strategy [79].

Extensive preclinical and clinical findings strongly suggest a compromise of the melanocortin system in bodyweight regulation [55]. Studies in genetically manipulated mice showed that elimination of α-MSH, overexpression of AgRP or MC-4 receptor knockout resulted in obesity [80]. Moreover, MC4-receptor activation also increases insulin sensitivity and energy expenditure, part of which effect is independent of food intake [81].

Strong interest has been put in the development of MC-4 receptor agonists. However, activation of hypothalamic MC4-receptors does not only regulate food intake, but also increases blood pressure and heart rate [82, 83]. Administration of MC4 receptor agonists is also associated with penile erections as well as flushing, limiting the potential utility of this novel therapeutic group for treatment of obesity [84].

Increasing energy expenditure may also be a therapeutic target for the design of anti-obesity drugs [55]. In this way, activation of adipose β3-adrenoceptors increases thermogenesis and lipolysis due to an increase in the expression of uncoupling protein 1(UCP1). β3-adrenoceptor agonists, such as N-5984, are currently under development [85]. A general problem of these agents is the fact that mitochondria-rich brown adipose tissue, which expresses UCP1, disappears in human beings after birth [55]. However, other authors suggest that brown fat cells reappear during chronic treatment with β3-adrenergic receptor agonists [86]. Therefore, further studies are needed to define the role of these agents in the treatment of obesity.

Regulation of the size of lipid stores by affecting lipogenesis or lipolysis may also represent an interestingly strategy for the design of new chemical entities with weight loss activity [55]. Acyl-CoA:diacylglycerol-acyltranferase-1 (DGAT-1) is a microsomal enzyme that promotes synthesis of triglyceride [87]. Partial inhibition of DGAT-1 has been shown to prevent diet-induced obesity in mice and to decrease adiposity through a mechanism involving enhanced energy expenditure [88]. Zhao *et al.* [89] designed and evaluated new chemical entities that partially inhibit DGAT-1 in diet induced obesity. After chronic administration of these compounds, a loss in bodyweight and liver triglycerides were observed in a dose/dependent manner, suggesting a potential role of DGAT-1 inhibitors as anti-obesity agents.

Human growth hormone fragment, AOD 9604, exerts a selective effect on adipose tissue promoting fat oxidation [55]. Contrary to human growth hormone, AOD 9604 does not induce diabetogenic and tumorigenic actions [90]. Preliminary studies with AOD 9604 have demonstrated that human growth hormone fragment increases energy expenditure and fat oxidation independently to a β3-adrenoceptor mechanism. Nevertheless, AOD 9604 increases β3-adrenoceptor expression, which may contribute to enhanced lipolytic activity [90].

Actually, weight loss effects of Oleoyl-estrone (OE) are under preclinical investigation. Administration of Oleoyl-estrone (OE) in rats induces loss of body fat, without reduction of body protein [91, 92]. OE is synthesized from estrone by adipose tissue [93] and released into the bloodstream [94, 95]. Short-term actions of OE involve the decrease in food intake, decrease in body weight and an impressive decrease of cholesterol levels, mainly due to the sharp decrease of HDL-cholesterol that results from an increased cholesterol turnover rate [96]. The negative effect on HDL-C concentration represents a great limitation for the use of OE in the treatment of obesity.

Finally, a recent article determined that adipocyte number in human adipose tissue is determined since early adulthood, as a consequence of a precise balance between new adipocites generation and adipocite death [97]. Interestingly, this number is not affected in the adulthood by changes in body weight, and obese patients have a greater number of adipose cells than lean subjects since early stages of life. Taking into account that the number of adipocites in obese patients might be involved in leptin deficiency after weight loss (and, in consequence, increase therapeutic failure), it is expected that in the near future new agents will be developed in order to modulate adipocite turnover.

CONCLUSION

In conclusion, although current anti-obesity agents are useful and relatively safe, there are many limitations (in efficacy as well as in safety profiles) that need to be overcome by next generation drugs. Fortunately, several pharmacological targets for the treatment of obesity have been identified, resulting in the development of a great number of investigational drugs aimed to be used for weight loss in clinical practice. However, most of these compounds are still under development and their clinical efficacy needs to be proven.

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