



Review

Rimonabant: an antagonist drug of the endocannabinoid system for the treatment of obesity

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Abstract:

Obesity, an ever-increasing problem in the industrialized world, has long been a target of research for a cure or, at least, control of its expansion. In the search for treatment, the recently discovered endocannabinoid system has emerged as a new target for controlling obesity and its associated conditions. The endocannabinoid system plays an important role in controlling weight and energy balance in humans. This system is activated to a greater extent in obese patients, and the specific blockage of its receptors is the aim of rimonabant, one of the most recent drugs created for the treatment of obesity. This drug acts as a blockade for endocannabinoid receptors found in the brain and peripheral organs that play an important role on carbohydrate and fat metabolism. Clinical studies have confirmed that, when used in combination with a low calorie diet, rimonabant promotes loss in body weight, loss in abdominal circumference, and improvements in dyslipidemia. Rimonabant is also being tested as a potential anti-smoking treatment since endocannabinoids are related to the pleasurable effect of nicotine. Thus, rimonabant constitutes a new therapeutic approach to obesity and cardiovascular risk factors. Studies show effectiveness in weight loss; however, side effects such as psychiatric alterations have been reported, including depression and anxiety. These side effects have led the FDA (Food and Drug Administration) to not approve this drug in the United States. For a more complete evaluation on the safety of this drug, additional studies are in progress.

Key words:

endocannabinoids, obesity, rimonabant, psychiatric alterations

Introduction

In industrialized world, obesity has become a health problem of epidemic proportions. This condition is an important risk factor that interferes with the treatment of pathologies such as diabetes, hypertension, and

other cardiovascular diseases, which present a high mortality rate [1, 31]. Bearing in mind the consequences on the health of human beings, obesity has been the target of studies for many years and is considered difficult to control in the modern world. The effectiveness of treatments is extremely important. However, many of the alternatives available, such as

low calorie diets and appetite-suppressant drugs, frequently fail [1, 31, 39]. Most studies that report weight loss after obesity treatments composed merely of low calorie diets have shown disappointing results. Most patients regain the weight lost, partially or completely, within 3 to 5 years after treatment. Long-term studies present an even less favorable profile [13]. Gosselin and Cote have followed women for 11 years after their weight loss and showed that 49.5% had regained or even surpassed their previous weight [21]. These limitations in treatment efficacy have led to the development of new strategies in maintaining weight loss, such as the use of pharmacotherapy [13].

The action of cannabinoids present in marijuana, more specifically of Δ -9-tetrahydrocannabinol (THC), is widely known, whether it comes from therapeutic use or from drug abuse [8]. One of the most significant effects of marijuana and endogenous cannabinoids is the excessive stimulation of the appetite, which occurs right after consumption. This effect, associated with the discovery of cannabinoid receptors and endocannabinoids, contributes to clarifying the role of these elements in regulating eating behavior, energy balance, and the storage and metabolism of glucose and lipids [10, 14, 20]. Several studies have been conducted to clone and characterize cannabinoid receptors, as well as to evaluate the mechanisms of cannabinoid action involved in metabolic disorders [9, 24].

In the 1990's, two endogenous agonists of cannabinoid receptors were discovered: N-arachidonoyl ethanolamine (anandamide) and 2-arachidonoyl glycerol (2-AG), which are currently designated as endocannabinoids. The first specific cannabinoid CB1 receptor antagonist was named SR 141716 or rimonabant, and the first specific CB2 antagonist receptor was named SR 144528 [18].

This work presents a review of the localization of cannabinoid receptors in the human body, the action of endocannabinoids in relation to appetite stimulation, and the pharmacological characteristics of rimonabant.

Receptors

After their discovery in the late 1980s, the cannabinoid receptors were named CB1 and CB2. They be-

long to the G-protein coupled receptor superfamily. Their activation typically leads to inhibition of adenylyl cyclase, consequently closing calcium channels, opening potassium channels, and stimulating protein kinase A. The distribution in the human body varies according to the different receptor subtypes, and their localization is directly linked to the type of action carried out by endocannabinoids at that site [10, 18, 38].

CB1 receptors are abundant in the central nervous system (basal ganglia, hippocampus, cerebral cortex, and hypothalamus), peripheral nervous system, gastrointestinal system, reproductive system, cardiovascular system, and adipose tissue [10, 11, 38]. CB1 receptors modulate dopamine release induced by THC, opioids, and nicotine, while regulating pain perception [9, 10]. The receptors are directly involved in the orexigenic effect of endocannabinoids as well as in the regulation of metabolism, body weight, and insulin resistance, and are, therefore, the main targets in the development of new drugs for obesity treatment [4, 29].

CB2 receptors are found in immune system cells, especially in B-cells and macrophages. This localization is directly coupled to the action of these receptors in the suppression of pro-inflammatory cytokine expression [38].

Endogenous ligands

Discovered five years after the CB1 and CB2 receptors, endocannabinoids are derived from esters, ethers, and amides of long chain polyunsaturated fatty acids, particularly arachidonic acid [9, 10].

The main endocannabinoids are anandamide and 2-AG, which function as neurotransmitters or neuromodulators. They are produced where and when necessary, are metabolized immediately after their action is finalized, and are not stored in neurons. Some of the effects of these ligands are related to food intake and energy balance control including peripheral and central orexigenics. Anandamide and 2-AG can be found in the hypothalamus, a region responsible for controlling food intake [24]. They stimulate food intake when released in the hypothalamic nucleus and nucleus accumbens, which are regions associated with food motivation. Hypothalamic sensitivity to hyperphagia induced by anandamide and 2-AG explain

the important role of endocannabinoids in food control [14]. There are other endocannabinoids, such as noladin ether and virodhamine, which have less effect on food intake [9, 38].

Due to the broad distribution of cannabinoid receptors, many researchers are looking for mechanisms of action in different physiopathological processes. Animal studies have shown that endocannabinoids are effective against chronic pain, they reduce spasms and tremors resulting from multiple sclerosis, and they can potentially reduce tumor growth. Other recent studies have also explored the actions of endocannabinoids and their receptors on gastrointestinal, mental, cardiovascular, and ocular pathologies [28].

Rimonabant – antagonist of the endocannabinoid system

General characteristics

Rimonabant, also known as SR141716, was described in 1994 by Rinaldi-Carmona et al. [32]. Because it acts on abdominal fat, it became popularly known as the ‘anti-beer belly pill’. It is the first known substance to block CB1 receptors and is 99% linked to plasma proteins. It is metabolized by cytochrome P450 in the liver and is almost completely expelled in the feces. It may interact with other drugs metabolized by cytochrome P450, especially those biotransformed by isoforms CYP 2A6, 2C9, 2C19, and 3A4 [11]. Some CYP3A4 inhibitors, like ketoconazole, lead to an increase in rimonabant blood levels, while CYP3A4 inducers decrease plasma concentrations and consequently lead to loss in rimonabant effectiveness [41].

Rimonabant antagonizes anandamide-, 2-AG-, and THC-induced hyperphagia. It selectively decreases the intake of savory drink and food (products that are rich in carbohydrates and lipids), the intake of which are generally increased in obese patients, which indicates that central cannabinoid system blockage can alter the pleasure response induced by food intake and therefore, reduce the quantity of ingested food [31].

Pre-clinical studies

The rimonabant effect on food intake occurs in humans as well as in animals, which is why the use of

rats and mice in the test phase was considered an appropriate experimental model. In recent years, two main experimental models have helped scientists in their search for the mechanisms of action of the endocannabinoid system on peripheral metabolic functions: the development of mice with CB1 receptor deletion, and diets that induce obesity in genetically modified rodents [30]. In one of the studies carried out using these models, two groups of mice – the first with CB1 receptors (CB1 (+/+)), and the second with the CB1 receptor deleted (CB1 (-/-)) – were used to analyze the role of CB1 receptors while being submitted to a fat-rich diet. The CB1 (+/+) mice apparently began to suffer from the same metabolic syndrome observed in humans. The CB1 (-/-) mice resisted the obesity induced by a fat rich diet and presented a more favorable metabolic profile in comparison to the controls with cannabinoid receptor deletion [27, 38].

Recently, Herling et al. [22] showed that rimonabant treatment resulted in elevated free fatty acids postprandially, demonstrating that rimonabant could induce lipolysis and that it did not act secondarily and postabsorptively due to reduced food intake. The weight-reducing effect of rimonabant was thus determined to be due to continuously elevated energy expenditure based on increased fat oxidation driven by lipolysis from fat tissues as long as fat stores were elevated. When the amount of endogenous fat stores declined, the rimonabant-induced increased energy expenditure was maintained by a re-increase in food intake.

Gary-Bobo et al. [15] have shown the liver-protecting effect of rimonabant and its potential clinical use in obesity-related liver disorders. This study consisted of treating obese mice daily with rimonabant (30 mg/kg) over a period of 8 weeks. Treatment reduced hepatomegaly, the plasma levels of enzyme markers of liver damage (alanine aminotransferase, gamma-glutamyl transferase, and alkaline phosphatase), and the high levels of TNF- α associated with steatohepatitis. The effects on the lipid profile were also evaluated and reinforced data from other studies that showed improvements in dyslipidemia through the reduction of triglyceride, free fatty acid and total cholesterol levels, and the increase of the HDL/LDL ratio.

Cross-talk between cannabinoids and other systems controlling appetite might exist since cannabinoid receptors are present in hypothalamic neural circuits involved in feeding regulation and energy expenditure.

Orexin A-hypocretin 1, an orexigenic peptide, is a candidate to interact with cannabinoid receptors. Both play an important role in feeding and are co-localized in similar brain regions [5]. Crespo et al. [5] showed that cannabinoid and orexin A-hypocretin 1 systems share a common mechanism in food intake and indicate that the hypothalamic orexigenic circuits are involved in the cannabinoid CB1 receptor antagonism-mediated reduction of appetite.

Clinical trials

In humans, broad clinical tests in phase I, II, and some in phase III have already been concluded, and others are still in progress. The goal of phase III is to prove by final evaluation the effectiveness of a new treatment, especially in comparison to other current alternatives. If the drug presents satisfactory test results, it will be submitted for review by regulatory authorities from multiple countries [6, 16, 30, 36].

In one of the most important rimonabant studies, testing was divided into four groups – “Rimonabant in Obesity (RIO)”: RIO-Lipids [6], RIO-North America [30], RIO-Europe [36], and RIO-Diabetes [33]. The goal was to evaluate the role of rimonabant in obesity management, weight loss maintenance, weight regain prevention after initial weight loss, and improvement of obesity-related risk factors, such as diabetes and dyslipidemia. These four studies assessed the effects of the drug on cardiometabolic risk factors in overweight or obese patients. The RIO-Lipids study was a multicenter, randomized, double-blind, placebo-controlled, parallel group, fixed-dose, one-year international study, which compared treatments of 20 mg/day or 5 mg/day of rimonabant to placebo in a group of 1,036 overweight or obese patients that had untreated dyslipidemia. The study results showed that patients treated with one daily dose of 20 mg of rimonabant exhibited a significant reduction in many cardiometabolic risk factors. The changes observed included triglyceride level reduction and HDL cholesterol increase, abdominal circumference and body weight reduction, glucose tolerance improvement, and blood pressure decrease. Other important findings were also observed regarding emerging risk markers, including an increase in adiponectin, a protein associated with a reduced risk of diabetes and heart disease and a decrease in C-reactive protein (CRP), an inflammation marker associated with cardiovascular risks. A relevant statistical analysis suggested that the

increase in adiponectin observed in the clinical study was beyond any expected improvement, which could be a result of isolated weight loss, increasing the potential of rimonabant's direct effect on this risk marker [6].

The methodology used in other RIO studies – RIO-North America, RIO-Europe, and RIO-Diabetes – was the same, differing only in number and type of patients studied and the research location. RIO-Diabetes involved patients with type II diabetes in treatment for over six months. RIO-Europe studied non-diabetic patients with hypertension or dyslipidemia, and RIO-North America evaluated patients from the US and Canada that presented dyslipidemia and abdominal obesity, as in RIO-Lipids.

A two-year study allows for assessment of the durability of the improvements such as weight loss, waist reduction, and several cardiometabolic risk factors in patients that continue the treatment with rimonabant. In RIO-North America, similar results were found in the group of patients who received 20 mg of rimonabant during year 2. In addition to weight loss, rimonabant therapy was associated with significant improvements in lipid and glycemic variables. Whereas the improvements in HDL-C and triglyceride levels were observed concomitantly with a greater reduction in body weight during year 1, such improvements in the rimonabant 20 mg group persisted during year 2 when body weight was almost stable. Consistent with the year 1 results, the improvement in HDL-C and triglyceride levels exceeded the changes attributable to weight loss alone. This direct peripheral effect of rimonabant on HDL-C and triglyceride levels may be related to enhanced adiponectin mRNA expression in adipose tissue and changes in hepatic enzymes regulating lipid metabolism [35, 37].

The data from the RIO studies indicate that rimonabant is effective in maintaining weight loss for a two-year period minimum, and also that it is well-tolerated in long-term treatments [35, 37].

Adverse events

In addition to the effects on appetite regulation, rimonabant has also caused side effects in patients. These effects can be divided into three main groups: psychiatric alterations, like depression, anxiety, and irritability; gastrointestinal disorders manifested in the form of nausea; and neurological alterations, like headaches and vertigo [6, 11, 16]. Since obesity is

commonly linked to depression and anxiety symptoms, rimonabant treatment should only be started after these pathologies are controlled. One of the main causes for discontinuation of treatment with this antagonist is side effects such as depression or anxiety [11].

Christensen et al. [3] carried out a study of databases until July of 2007. Data from four randomized, double-blind studies were evaluated, comparing 20 mg of rimonabant and a placebo. According to the authors, until the end of the study, all four published studies showed greater weight loss with rimonabant treatment when compared to the placebo. However, little concern was expressed regarding drug tolerance or safety issues.

Studies analyzed by Christensen et al. [3] included Rimonabant in Obesity Europe, Lipids, North America, and Diabetes and were sponsored by Sanofi-Aventis. For mood analysis, the *hospital anxiety and depression scale* (HADS) score was used at the beginning of the trial and later in every three months. Questions about suicidal thoughts were not asked. There was no significant difference between the groups in regards to depression; yet, the numbers of those experiencing anxiety were larger in the rimonabant group. Only in the RIO-Lipids study were symptoms of depressive mood, depression, and severe depression characterized. In other RIO studies, only depressive mood was characterized. A larger number of psychiatric alteration cases were reported in the rimonabant group in comparison to the placebo group. Rimonabant patients were two to five times more likely to discontinue treatment than placebo group patients. Possible factors contributing to this finding were studied in order to relate early treatment data to any side effects after treatment. An association was established between high triglyceride levels at the beginning of the treatment and the development of depressive mood. An association was also established between higher age and an increased probability of side effects.

Després et al. [7] said that patients switching from rimonabant 5 mg or 20 mg to placebo regained weight to a level comparable with that of patients treated with nutritional recommendations alone for two years. However, the beneficial effects of rimonabant on bodyweight, waist circumference, HDL cholesterol, and triglycerides were maintained (in RIO-North America and RIO-Europe) during two years of continuous rimonabant treatment. This confirms the well established principle that, as with chronic diseases such as hypertension or diabetes, maintenance of efficacy requires treatment continuation [7].

The Rimonabant in Obesity (RIO)-Europe study concluded that rimonabant was well-tolerated and caused few side effects; however, individual studies have shown an increased tendency of patients to exhibit depressive moods, depression and anxiety [3].

There are some disagreements between Christensen et al. [3] and the authors of the RIO studies about efficacy and safety of rimonabant. Després et al. [7] argue that the protocols specifically excluded only patients with “clinically significant psychiatric disease and history of severe depression that could be defined as depression leading the patient to be hospitalized, or patients with two or more recurrent episodes of depression, or a history of suicide attempt”. The response of Astrup et al. [2] (Christensen’s research group) to Després et al. stated that they could not find the cited wording of the exclusion criteria anywhere, neither in the protocol information at ClinicalTrials.gov nor in the RIO publications. In the RIO-North America publication, the exclusion criteria were “any clinically significant neuropsychiatric disorders” and in RIO-Diabetes “any clinically significant disorder” and “use of any medication known to affect bodyweight (e.g. antidepressants)” [2, 7].

According to Christensen et al. [3], psychiatric effects of rimonabant should be studied more intensely and carefully. Thus far, the limitations and the risk for severe psychiatric effects have not been analyzed. Two suicide cases were reported, one in RIO-North America – in which the patient was taking 5 mg of rimonabant – and another in a study that is still in progress – in which the patient was taking 20 mg of rimonabant [3]. A recent publication reports four suicides in patients taking rimonabant [2].

According to Mitchell et al. [26], the FDA suggests that the results presented by Christensen et al. [3] are still underestimated, and that the psychiatric effects of rimonabant are more severe and more frequent than those described. The FDA showed that 26% of participants taking 20 mg of the drug presented with psychiatric side effects (mainly depression and anxiety) in comparison to 14% from the placebo group. The FDA found substantial evidence that the participants taking 20 mg had greater risk for suicidal thoughts and attempts than placebo patients.

Després et al. [7] criticize the findings of the US FDA regarding the increased odds ratio of suicidality in patients treated with rimonabant by saying that “suicidal ideation” has not clearly been shown to translate into a higher rate of suicide. Astrup et al. [2]

replied to this critique by saying that “suicidal ideation” is not the same as suicide, however, it is considered to be a risk factor for suicide [2, 7].

Mitchell et al. [26] report that these clinical findings coincide with those of animal studies, which suggest that endocannabinoids have an antidepressant and anxiolytic effect. In this case, the inhibition of anandamide hydrolysis (endogenous cannabinoid) has an antidepressant effect, and such effect is blocked by rimonabant [17].

To better define the efficacy and safety of rimonabant, Van Gaal et al. recently selected efficacy data from the RIO-Diabetes study, and pooled safety data for all four RIO studies [35]. At one year, gastrointestinal, neurological, and psychiatric adverse events were more frequently reported with rimonabant treatment than with placebo. Serious adverse events were infrequent and almost equivalent to placebo. Overall discontinuation rates were similar across treatment groups, except discontinuation from adverse events, which occurred more frequently with 20 mg rimonabant than placebo (most commonly, depressive disorders [1.9 vs. 0.8%], nausea [1.4 vs. 0.1%], mood alterations with depressive symptoms [1.0 vs. 0.6%], and anxiety [1.0 vs. 0.3%]). An examination of the long term effect of rimonabant in two year results from the RIO-Europe study revealed that most of benefits observed at year 1 were maintained during year 2, with little evidence of body weight regain and no attenuation of the improvements in cardiometabolic risk factors. This study confirmed the results of the meta-analysis of Christensen et al. [3], which reported an overall increased risk of depression in RIO clinical trials (one year), but showed that the incidence of depressed mood disorders and disturbances was low and similar between placebo and 20 mg rimonabant during year 2 [37]. According to Van Gaal et al., these studies show that rimonabant was generally well-tolerated in the four pooled RIO studies with a defined safety profile, but the authors suggest that particular attention to the occurrence of recurrent depression is needed [35, 37].

The use of rimonabant for obesity treatment should be carefully considered. These studies and discussions are beneficial and extend the research that focuses on the safety and efficacy of this drug. However, it is important to have a better knowledge of its long term effects. Research has shown that 48% of obese individuals exhibited depression and that, in comparison

to non-obese women, obese women are 20% more likely to present suicidal thoughts and 23% more likely to have attempted suicide previously [19, 40]. Since obese people are the target population of these studies, the incidence of psychiatric adverse effects resulting from these drugs should be considered.

Pharmacological treatment for obesity and legislation

All medication used in obesity treatments must be effective in reducing body weight. Studies of these medications must provide evidence that the side effects are tolerable and/or temporary, provide long-term effectiveness and safety data, and offer a known mechanism of action [25].

The first centrally-acting drugs (appetite suppressants) were amphetamine, methamphetamine, and phenmetrazine. These are no longer an option due to their high addiction potential. Inhibitors of 5-hydroxytryptamine (5-HT) uptake, fenfluramine and dexfenfluramine, were approved for obesity, but were implicated in cases of pulmonary hypertension and increased valvular heart disease and, therefore, were taken off the market [13].

The current pharmacological treatments are divided into two classes: drugs with central action, such as amfepramone, femproporex, and sibutramine, and drugs with peripheral action, such as orlistat. Amfepramone and femproporex, which are forbidden in many countries, act by increasing levels of catecholamines and inhibiting appetite. Their main disadvantage is the risk of causing drug dependency. Sibutramine stimulates the sensation of satiety and increases energy expenditure; its main side effects are increased blood pressure and tachycardia. Orlistat acts peripherally by inhibiting intestinal absorption of ingested fat. The main side effects are fecal incontinence and interference in liposoluble vitamin absorption, thus requiring supplementation [23]. Cardiovascular adverse effects, such as hypertension and tachycardia, limit the use of these agents, especially in patients with cardiac comorbidities [34]. All drugs have been proven to be effective in obesity control. Nevertheless, when compared to rimonabant, they are less effective in the controlling of cardiovascular risk factors.

Drugs such as phendimetrazine, phentermine, amfepramone, mazindol, and benzphetamine are being commercialized. They were, however, classified by the FDA (Food and Drug Administration) as sub-

stances recommended only for short-term treatment. The only FDA approved drugs for long-term treatment are orlistat and sibutramine [13].

In June 13th of 2007, the FDA board, based on a data review presented in 2005, failed to approve rimonabant and concluded that this medication is effective for weight control, but that there was not enough evidence to evaluate or assess the potential risks of the drug. The FDA is particularly concerned about the association between rimonabant and psychiatric side effects, including depression and suicide, and neurological side effects, such as the risk of convulsions [12]. Still, the use of this drug is allowed in the European Community.

Final considerations

There are several drugs available for treating obesity; however, the pharmacological treatment is only justified when combined with a change in the patient's eating habits and life style. In addition, it is necessary to be aware that the drug treatment does not 'cure' obesity. When treatment is concluded, if patients do not change their eating habits and lifestyle, weight gain is usually inevitable.

The blockage of the CB1 receptor comes as a new alternative for treating obesity and other associated risks because it enables weight loss and still helps control of other risk factors, such as reducing lipogenesis, abdominal circumference, insulin resistance, and dyslipidemia. However, in order to receive approval for this drug by regulatory entities, its long-term effectiveness and safety profile should be well-clarified.

References:

1. Aronne LJ, Thornton-Jones ZD: New targets for obesity pharmacotherapy. *Clin Pharmacol Ther*, 2007, 81, 748–752.
2. Astrup A, Christensen R, Bartels EM, Bliddal H: Efficacy and safety of the weight-loss drug rimonabant – Authors' reply. *Lancet*, 2008, 371, 556–557.
3. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A: Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomized trials. *Lancet*, 2007, 370, 1706–1713.
4. Cota D, Marsicano G, Grübler Y, Tschöp M, Grübler Y, Flachskamm C, Schubert M, Auer D et al.: The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest*, 2003, 112, 423–431.
5. Crespo I, Gómez de Heras R, Rodríguez de Fonseca F, Navarro M: Pretreatment with subeffective doses of rimonabant attenuates orexigenic actions of orexin A-hypocretin 1. *Neuropharmacology*, 2008, 54, 219–225.
6. Després, JP, Golay, A Sjöström, L: Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med*, 2005, 353, 2121–2134.
7. Després JP, Van Gaal L, Pi-Sunyer X, Scheen A: Efficacy and safety of the weight-loss drug rimonabant. *Lancet*, 2008, 371, 555.
8. Di Marzo V, Goparaju SK, Wang L, Liu J, Bátkai S, Jári Z, Fezza F et al.: Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature*, 2001, 410, 822–825.
9. Di Marzo V, Melck D, Bisogno T, De Petrocellis L: Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends Neurosci*, 1998, 21, 521–528.
10. Ducobu J: The endocannabinoid system and the regulation of the metabolism (French). *J Pharm Belg*, 2005, 60, 84–88.
11. Ducobu J, Sternon J: Rimonabant (Acomplia), specific inhibitor of the endocannabinoid system. *Rev Med Brux*, 2005, 26, 165–168.
12. Food and Drug Administration (FDA). Briefing Document. Advisory Committee – June 13, 2007. Available in: <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-fda-backgrounder.pdf>.
13. Fortes RC, Guimarães NG, Haack A, Torres AAL, Carvalho KMB: Orlistat and sibutramine: good aid for loss and maintenance of weight (Portuguese)? *Rev Bras Nutr Clin*, 2006, 21, 244–251.
14. Fride E, Bregman T, Kirkham T: Endocannabinoids and food intake: newborn suckling and appetite regulation in adulthood. *Exp Biol Med*, 2005, 230, 225–234.
15. Gary-Bobo M, Elachouri G, Gallas JF, Janiak P, Marini P, Ravinet-Trillou C, Chabbert M et al.: Rimonabant reduces obesity-associated hepatic steatosis and features of metabolic syndrome in obese Zucker fa/fa rats. *Hepatology*, 2007, 122–129.
16. Gelfand EV, Cannon CP: Rimonabant: a cannabinoid receptor type 1 blocker for management of multiple cardiometabolic risk factors. *J Am Coll Cardiol*, 2006, 47, 1919–1926.
17. Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, Solinas M, Cassano T et al.: Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proc Natl Acad Sci USA*, 2005, 102, 18620–18625.
18. Godoy-Matos AF, Guedes EP, Souza LL, Valério CM: The endocannabinoid system: a new paradigm in the metabolic syndrome treatment (Portuguese). *Arq Bras Endocrinol Metab*, 2006, 50, 390–399.
19. Goldsmith SJ, Anger-Friedfeld K, Beren S, Rudolph D, Boeck M, Aronne L: Psychiatric illness in patients pre-

- senting for obesity treatment. *Int J Eat Disord*, 1992, 12, 63–71.
20. Gómez R, Navarro M, Ferrer B, Trigo JM, Bilbao A, Del Arco I, Cippitelli A et al.: A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. *J Neurosci*, 2002, 22, 9612–9617.
 21. Gosselin C, Cote G: Weight loss maintenance in women two to eleven years after participating in a commercial program: a survey. *BMC Womens Health*, 2001, 1–2.
 22. Herling AW, Kilp S, Elvert R, Haschke G, Kramer W: Increased energy expenditure contributes more to the body weight reducing effect of rimonabant than reduced food intake in candy-fed Wistar rats. *Endocrinology*, 2008, 149, 2557–2566.
 23. Lean M, Mullan A: Obesity: Which drug and when? *Int J Clin Pract*, 2007 61, 1555–1560.
 24. Lutz B: The endocannabinoid system: linking body weight, metabolic disorders and tobacco dependence. *Diabetes Voice*, Belgium, 2005. Available in: <http://www.diabetesvoice.org/search/?a=337>, Accessed in: September 04, 2007.
 25. Mancini MC, Halpern A: Pharmacological treatment of obesity (Portuguese). *Arq Bras Endocrinol Metab*, 2002, 46, 497–513.
 26. Mitchell PB, Morris MJ: Depression and anxiety with rimonabant. *Lancet*, 2007, 370, 1671–1672.
 27. Pagotto U, Cervino C, Vicennati V, Marsicano G, Lutz B, Pasquali R: How many sites of action for endocannabinoids to control energy metabolism? *Int J Obes (Lond)*, 2006, 30, S39–43.
 28. Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R: The emerging role of the endocannabinoid system in endocrine regulation and energy balance. *Endocr Rev*, 2006, 27, 73–100.
 29. Juan-Picó P, Fuentes E, Bermúdez-Silva FJ, Javier Díaz-Molina F, Ripoll C, Rodríguez de Fonseca F, Nadal A: Cannabinoid receptors regulate Ca^{2+} signals and insulin secretion in pancreatic beta-cell. *Cell Calcium*, 2006, 39, 155–162.
 30. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J: Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA*, 2006, 295, 761–775.
 31. Ravinet Trillou C, Arnone M, Delgorge C, Gonalons N, Keane P, Maffrand JP, Soubrié P: Anti-obesity effect of SR141716, a CB1, receptor antagonist, in diet-induced obese mice. *Am J Physiol Regul Integr Comp Physiol*, 2003, 284, R354–R353.
 32. Rinaldi-Carmona M, Barth F, Héaulme M, Shire D, Calandra B, Congy C, Martinez S et al.: SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Lett*, 1994, 350, 240–244.
 33. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF: Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomized controlled study. *Lancet*, 2006, 368, 1660–1672.
 34. Steinberg BA, Cannon CP: Cannabinoid-1 receptor blockade in cardiometabolic risk reduction: safety, tolerability, and therapeutic potential. *Am J Cardiol*, 2007, 100, 27–32.
 35. Van Gaal LF, Pi-Sunyer X, Després JP, McCarthy C, Scheen A: Efficacy and safety of rimonabant for improvement of multiple cardiometabolic risk factors in overweight/obese patients: pooled 1-year data from the Rimonabant in Obesity (RIO) program. *Diabetes Care*, 2008, 31, S229–240.
 36. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S: Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet*, 2005, 365, 1389–1397.
 37. Van Gaal LF, Scheen AJ, Rissanen AM, Rössner S, Hanotin C, Ziegler O: Long-term effect of CB1 blockade with rimonabant on cardiometabolic risk factors: two year results from the RIO-Europe Study. *Eur Heart J*, 2008, 29, 1761–1771.
 38. Vickers SP, Kennett G: Cannabinoid and the regulation of ingestive behaviour. *Curr Drug Targ*, 2005, 6, 215–223.
 39. Wadden, TA: Treatment of obesity by moderate and severe caloric restriction. Results of clinical research trials. *Ann Intern Med*, 1993, 19, 688–693.
 40. Wadden TA, Sarwer DB, Womble LG, Foster GD, McGuckin BG, Schimmel A: Psychosocial aspects of obesity and obesity surgery. *Surg Clin North Am*, 2001, 81, 1001–1024.
 41. Wierzbicki AS: Rimonabant: endocannabinoid inhibition for the metabolic syndrome. *Int J Clin Pract*, 2006, 60, 1697–1706.

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