Cannabinoids and cardiometabolic risk

Csaba Farsang[1], Zoltán Járai[2]

[1]St. Imre Teaching Hospital, Cardiometabolic Centre, Budapest, Hungary
[2]Semmelweis University, 1st Department of Internal Medicine, Budapest, Hungary

Submitted: 22 December 2008
Accepted: 21 January 2009

Arch Med Sci 2009; 5, 2A: S 273– S 281
Copyright © 2009 Termedia & Banach

Corresponding author:
Csaba Farsang MD, DSc
Cardiometabolic Centre
St. Imre Teaching Hospital
Budapest XI. Tétényi u. 12-16
Hungary, H-1115
E-mail: hunghyp@t-online.hu

Abstract

The regulatory role of the endocannabinoid system has been implicated in many physiological and pathological functions and as a consequence the modulation of function of this system has become a therapeutic target in various diseases and pathological states. The authors give an overview of the pharmacological background of the endocannabinoid system and a short summary of the most important preclinical data. The connection between the endocannabinoid system and cardiometabolic risk is also discussed. Finally, landmark human studies with the cannabinoid antagonist rimonabant – such as the RIO, SERENADE, ARPEGGIO, STRADIVARIUS and ADAGIO-LIPIDS studies – are also reviewed.

Key words: endocannabinoid system, cardiometabolic risk, rimonabant, energy balance.

Introduction

The medicinal use of the extract of the plant *Cannabis sativa* (marijuana) goes back more than three thousand years in history. Besides its use as a well-known psychotropic agent, it was a popular painkiller in ancient China and an anxiolytic drug in India. Although the different properties of marijuana have been known for thousands of years, scientific research on the effects of the marijuana constituents – called cannabinoids – has begun only in the last few decades.

The identification of the endocannabinoid system was a breakthrough discovery. The generation of endogenous cannabinoid ligands (endocannabinoids) and the expression of the cannabinoid receptors and/or endocannabinoid metabolizing enzymes have been described in most tissues both in experimental animals and in humans, and have been implicated in the regulation of various physiological and pathological functions. Recent studies have also established a firm connection between the dysregulation of the endocannabinoid system and numerous major diseases and pathological states. Thus, the modulation of the endocannabinoid system has become an appealing therapeutic target in various diseases.

Cannabinoid receptors and cannabinoid receptor antagonists

The first major step in the discovery of the endocannabinoid system was the identi-fication of the most important psychoactive constituent of marijuana, Δ^9-tetrahydrocannabinol (THC) [1]. Experiments with THC and other synthetic analogues showed structural and stereo-selectivity that

supported a drug-receptor interaction. This was proven in the early 1990s, when two different cannabinoid receptors were cloned [2, 3]. Two splice variants of CB1 (CB_{1A} and CB_{1B}) are also known, but their expression has not been reported [4]. Besides the fact that the cannabinoid-1 (CB_1) receptor is one of the most abundant receptors of the mammalian brain, its presence has been demonstrated in many peripheral cells and tissue (myocardium, postganglionic autonomic nerve terminal, vascular endothelium, vascular smooth muscle cells, adipocytes, liver, skeletal muscle) (for review see [4]). The localization of the cannabinoid-2 (CB_2) receptor is different. Initially it was considered to be expressed mainly in the cells of the haematopoietic and immune systems [3]. However, CB_2 receptors have recently been found in various other tissues, e.g. in the central nervous system, liver, myocardium, human coronary endothelial cells, smooth muscle cells, pancreas and bone [4].

The cannabinoid receptor signalling mechanism is very complex. Both CB_1 and CB_2 are G-protein coupled receptors. They have seven transmembrane domains containing the cannabinoid binding site and couple primarily to the $G_{i/o}$ subtypes of G proteins [4], causing inhibition of adenylate cyclase; however there are data for activation of adenylate cyclase and coupling to $G_{q/11}$ protein as well [5]. Through the G-protein mechanism cannabinoids activate different potassium channels and inhibit calcium channels [6]. Cannabinoids activate the multifunctional mitogen activated protein kinases (p44/42 MAP kinase, JUN terminal kinase, phosphatidylinositol-3-kinase) (for review see [4]). An important finding is the agonist selective activation of different G-protein subunits allowing the possibility of selective action of different agonists according to the different pattern of G-protein subunit expression [7].

Pharmacological evidence suggests that there are more additional cannabinoid receptors. One of these putative receptors has endothelial localization and its activation results in vasodilation [8], while the other one is at a presynaptic site on glutamatergic nerves in the hippocampus [9]. Molecular proof of these binding sites is still lacking. Data have recently been published suggesting that GPR55 is another cannabinoid receptor; however the *in vivo* function of this receptor is elusive [10].

Despite the fact that the CB_1 and CB_2 receptors have only 44% homology, THC binds both receptors with similar affinity. In contrast, newly synthesized agonists and antagonists can specifically bind either to CB_1 or CB_2 receptors. The highly selective cannabinoid receptor antagonists (e.g. SR141716: rimonabant) for CB_1 [11], and SR144528 for CB_2 [12] and experiments involving genetically modified knockout mice [13] provided an important tool for the characterization of the function of these receptors in health and disease.

The endocannabinoids

Following the discovery of CB_1 and CB_2 receptors, endogenous lipid ligands for these receptors – called endocannabinoids – were identified. So far two endocannabinoids have been characterized best: arachidonyl ethanolamide (anandamide, from the Sanskrit word "ananda" = "bliss") isolated from porcine brain [14], and 2-arachidonoyl glycerol (2-AG), present both in the gut [15] and in the brain [16]. These lipid-like substances bind to cannabinoid receptors and mimic many of the biological actions of plant-derived cannabinoids [17, 18]. The basal level of 2-AG in the brain is a hundred times higher than that of anandamide [4]. Anandamide is a partial or full agonist of CB_1 (depending on the localization and biological response measured) and also binds with very low efficacy to CB_2 receptors. 2-AG is a full agonist at both cannabinoid receptors (for review, see [4]).

Anandamide is synthesized *in vivo* in the cell membrane from a membrane lipid precursor, from N-arachidonoyl phosphatidyl ethanolamide, through a multistep enzymatic process [19] containing parallel pathways and involving various enzymes, such as phospholipase D, phospholipase C, and phosphodiesterase [20]. The modulation of the activity of these enzymes may also emerge as a therapeutic target in the near future. The other endocannabinoid, 2-AG, is produced from diacylglycerol (DAG) by DAG-lipase (for review, see [4]).

Endocannabinoids are not stored, but produced on demand. After being released into the extracellular space the uptake of endocannabinoids by neurons and other cells is performed mainly by facilitated diffusion driven by a concentration gradient. The findings that anandamide uptake can be selectively inhibited by structural analogues suggest that this uptake mechanism involves a saturable transporter protein which remains to be identified [4].

Evidence emerging from experiments using fatty acid amid hydrolase (FAAH) inhibitors or FAAH knockout mice strongly suggests that *in vivo* FAAH is primarily responsible for the intracellular degradation of anandamide (for review, see [21]). Although 2-AG can also be degraded by FAAH *in vitro*, there is no evidence for such a mechanism *in vivo*. 2-AG is hydrolyzed by monoacylglyceride lipase (MGL) [22].

The cannabinoid receptors, the endocannabinoids, the enzymes involved in the production and degradation of endocannabinoids, and the putative membrane transporters responsible for their cellular uptake and possible release, together comprise the endocannabinoid system.

Endocannabinoid system and cardiometabolic risk

Accumulating recent evidence suggests a key role of the endocannabinoid system in various obesity-related metabolic and cardiovascular diseases. These effects involve both central and peripheral mechanisms. For example leptin and endocannabinoid interaction on food intake was demonstrated in wild type and CB_1 knockout mice, indicating that hunger-induced increase in food intake may be mediated by endocannabinoids through CB_1 receptors [23]. In genetically obese (leptin or leptin receptor defective) mice rimonabant significantly decreased food intake, demonstrating that the endocannabinoid system is involved in hyperphagia in these models [23]. The anatomical localization of the leptin-endocannabinoid interaction is probably in the lateral hypothalamus [24]. There may be other localizations in the brainstem and limbic forebrain, where the endocannabinoids mediate orexigenic effects [4].

Besides central mechanisms, peripheral effects of the endocannabinoid system are also involved in energy balance. Chronic treatment with rimonabant after a transient reduction of food intake causes sustained weight loss in diet-induced obese rodents, suggesting an increase in energy expenditure ([25], for review, see [26]). Many recent findings suggest that an important target of the endocannabinoid system is the adipose tissue itself. CB_1 receptors are expressed on adipocytes, where all the enzymes responsible for the biosynthesis and metabolism of endocannabinoids are present [27]. The activation of CB_1 receptors results in increased lipogenesis and decreased fatty acid oxidation in the adipose tissue [28], while CB_1 blockade can reverse these effects. Treatment with rimonabant also increases adiponectin expression, a hormonal stimulus for fatty acid β-oxidation leading to energy expenditure [29].

The other major peripheral target of the endocannabinoid system in obesity related diseases is the liver, where the blockade of CB_1 receptors can reverse hepatic steatosis [30]. It has recently been shown that mice with hepatocyte-specific deletion of CB_1 receptors in spite of a high fat diet develop much less steatosis, have normal lipid profile and do not develop insulin and leptin resistance [31].

As CB_1 receptors are also present on the skeletal myocytes it was obvious to assume that cannabinoid activation can influence insulin resistance by affecting skeletal muscle glucose uptake. Indeed, in an obese rodent model chronic treatment with rimonabant increased insulin-stimulated glucose uptake and phosphorylation in the soleus muscle, improving insulin resistance [32].

Cardiometabolic risk

Use of the term "metabolic syndrome" has recently been widely and extensively debated. Its five individual components – increased waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, elevated blood pressure, and elevated fasting glucose – frequently aggregate in the same individual. However, an analysis of two prospective studies (PROSPER, BRHS) did not find an association of the metabolic syndrome with cardiovascular risk in the elderly in spite of its significant relation to diabetes [33]; therefore it was thought to "*put yet another nail in the coffin of the metabolic syndrome*" [34]. On the other hand, these findings are in good agreement with the concept of cardiometabolic risk (CMR). Being aware of the fact that cardiovascular morbidity and mortality are still the largest burden in the world, an academic group (International Chair on Cardiometabolic Risk – ICCMR) has been formed to emphasise the importance of an early epidemiological survey and preventive measures in cardiometabolic risk, considered to be one of the major issues jeopardizing the present and forthcoming health status. This academic group's key objective is to organise and harmonise these activities with special regards to research, prevention, education and management of CMR, in the region: particularly to exchange epidemiological data, unify methodologies, and create a harmonised, well-controlled practical approach for individuals. Why it is absolutely necessary is substantiated by a new study showing that intensification of medication in the presence of several cardiometabolic risk factors, such as hypertension, dyslipidaemia, diabetes, and abdominal obesity, is often being pursued inappropriately [35, 36]. Drugs having beneficial effects on most cardiometabolic components were greatly needed. Antagonising CB_1 cannabinoid receptors in experimental animal models as well as in humans was shown to have a favourable effect on body weight, and lipid and glucose metabolism, so this new group of drugs seemed to have great clinical potential. Two drugs (rimonabant, taranabant) have been thoroughly investigated. Because of its many side effects taranabant did not reach approval for clinical practice and its further development was stopped. Rimonabant has been approved for clinical practice in Europe as it was shown to have favourable effects on abdominal obesity and also on lipid and carbohydrate metabolism. However, because of its psychiatric side effects (anxiety, depression) this drug has recently been withdrawn from the market.

Several human studies have provided valuable information on the effects of the CB_1 antagonist rimonabant on cardiometabolic risk factors. In the following section we summarize the most important results of these studies.

RIO North America Study

This was a double-blind, placebo-controlled trial including 3040 obese individuals who were randomized to treatment by placebo, or by 5 mg, or by 20 mg daily rimonabant. All three groups of patients had a reduced-calorie diet. After one year, patients in the rimonabant arms were re-randomized to either rimonabant or placebo to investigate if rimonabant's effects would be maintained following cessation of the drug. The primary end point of the study was the change in weight at one year and maintenance of weight changes at two years. Effects of rimonabant on lipid parameters (plasma level of HDL cholesterol and on triglycerides) were also studied.

After one year the completion rate was 309 (51%) patients in the placebo group, 620 (51%) patients in the 5 mg of rimonabant group, and 673 (55%) patients in the 20 mg of rimonabant group. As compared to the data in the placebo-treated group, in the rimonabant-treated patients on 20 mg/day dose the body weight significantly (P<0.001) decreased by 6.3 kg (vs. 1.6 kg), the waist circumference by 6.1 cm (vs. 2.5 cm), the plasma level of triglycerides by 5.3% (vs. 7.9% increase), and the HDL cholesterol increased by 12.6% (vs. 5.4%).

After two years, patients who stayed on the 20-mg dose of rimonabant maintained the same body weight and waist circumference, while those re-randomized to placebo gained weight to a nearly identical level of those who had been on placebo for two years. Effects of 20 mg/day rimonabant on lipid parameters at two years were greater than expected from the degree of weight loss, suggesting that the metabolic effects of rimonabant are independent of weight-loss effects.

Side effects were similar in all treatment groups, but withdrawal was slightly higher in the rimonabant groups than in the placebo group. The most common drug-related adverse event was nausea (11.2% for the 20 mg of rimonabant group vs 5.8% for the placebo group) [37].

RIO-Europe Study

The effects of rimonabant (5 or 20 mg once daily in addition to a low calorie diet) on body weight and cardiovascular risk factors in overweight or obese patients (body-mass index 30 kg/m^2 or greater, or body-mass index greater than 27 kg/m^2) with dyslipidaemia, hypertension or both were assessed by this randomized, double-blind, placebo-controlled trial. The primary efficacy endpoint was weight change from baseline after 1 year of treatment, but parameters characterizing lipid and carbohydrate metabolism were also investigated.

Weight loss at 1 year was significantly greater in patients treated with rimonabant 5 mg (mean –3.4 kg, P=0.002 vs. placebo) or 20 mg (–6.6 kg, P<0.001 vs. placebo) compared with placebo (–1.8 kg). Rimonabant (20 mg) produced significantly greater improvements than placebo in waist circumference, HDL cholesterol, triglycerides, and insulin resistance. The effects of rimonabant 5 mg were of less clinical significance. Rimonabant was generally well tolerated with mild and transient side effects. At two years 20 mg rimonabant induced a significant (P<0.001) decrease in waist circumference by 7.5 cm (vs. 3.4 cm by placebo), in body weight 7.2 kg (vs. 2.5 kg by placebo), in plasma level of triglycerides 8.8% (vs. 6.3% increase in placebo), and an increase in HDL cholesterol by 28.2% (vs. 16.8% by placebo) [38].

RIO-Diabetes Study

In the RIO-Diabetes study patients had type 2 diabetes that was poorly controlled with either metformin or a sulphonylurea, a body mass index of 27 to 40 kg/m^2, and were free of other clinically significant conditions (e.g. severe vascular complications of diabetes). Three hundred and 39 patients were randomized to receive rimonabant 20 mg/day, 358 to rimonabant 5 mg/day, and 348 patients to placebo treatment.

Patients in the 20 mg/day rimonabant-treated group lost significantly (P<0.0001) more weight and showed improvements in the ratio of total cholesterol /high-density-lipoprotein cholesterol (–0.51 vs. –0.16, respectively), triglycerides (–9.1 vs. + 7.3%, respectively), fasting glucose level (–0.64 vs. + 0.33 mg/dl), glycosylated haemoglobin (–0.6 vs. + 0.1%, respectively), and hsC-reactive protein (–1.4 vs. 0.0 mg/l, respectively) as compared to those in the placebo group. Patients in the 5 mg/day rimonabant group had statistically significant but less pronounced reductions in body weight and waist circumference and less changes in metabolic parameters. Rimonabant induced metabolic changes were independent of weight loss; therefore it was hypothesized that rimonabant has a direct modulating effect on such cardiovascular and metabolic risk factors/markers. Dropout rates were not different in the three groups. More people from the rimonabant group than from the placebo group withdrew because of adverse events (depressed mood disorders, nausea, and dizziness) [39].

RIO-Lipids Study

The RIO-Lipids double-blind, randomized trial aimed to extend observations from the RIO-Europe Study to show the benefits of rimonabant in overweight or obese individuals who had high risk of cardiovascular disease. One thousand and thirty-six overweight or obese (body mass indices

of 27 and 40) patients were included who had had untreated dyslipidaemia (triglyceride levels between 1.69 and 7.90 mmol/l) or had a ratio of total cholesterol/high-density lipoprotein cholesterol higher than 4.5 in women and 5.0 in men. The patients were treated with rimonabant 20 mg/day or placebo for 12 months.

As compared with placebo, rimonabant 20 mg significantly decreased body weight by 6.7 kg, waist circumference by 5.8 cm, increased HDL cholesterol by 10.0%, reduced triglycerides by 13.0%, and increased levels of adiponectin by 46.2%. Rates of study completion were low, with no significant differences between placebo- or rimonabant-treated group (62.6 vs. 63.9% respectively) [40].

A meta-analysis of studies with 20 mg/day rimonabant involving a total of 6625 [42] or 5580 [43] patients showed a significant weight loss (4.64-6.5 kg) and a reduction in waist circumference (3.84-6.4 cm). Statistically significant but minimal reductions in weight and waist circumference were also seen in the 5 mg/day group compared with placebo. Plasma levels of triglycerides were significantly reduced (by 19.82 mg/dl or by 6.9%), and HDL cholesterol was significantly increased (by 3.54 mg/dl or by 16.4%) in the 20 mg/day group compared with the placebo-treated patients. General adverse effects and serious adverse effects were significantly greater in the 20-mg group as compared with placebo: 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% [41, 42].

After 1 year of treatment with rimonabant 20 mg/day the mean reduction in systolic blood pressure from baseline was –0.8 mm Hg (0.3 mm Hg for placebo); that in diastolic blood pressure was –0.8 (–0.3 mm Hg for placebo). However, in the subgroup of hypertensive patients the change in systolic blood pressure was –7.5 mm Hg for rimonabant 20 mg/day vs. –4.7 mm Hg for placebo, and that for diastolic blood pressure was –5.2 mm Hg vs. –3.0 mm Hg in the placebo-treated group (P<0.001). Reductions were even more pronounced in patients with dyslipidaemia and type 2 diabetes. The effect of rimonabant 20 mg on blood pressure was thought to be related to the weight loss [42].

SERENADE Study

This was a 6-month, randomized, double-blind, placebo-controlled trial of rimonabant 20 mg/day in drug-naive patients with type-2 diabetes (HbA_{1c} 7-10%). The primary endpoint was the change of HbA_{1c} from baseline; secondary endpoints were changes in body weight, waist circumference and lipid profile. From 281 randomized patients 236 (84.9%) completed the study. Baseline HbA_{1c} (7.9%) was reduced by –0.8% with rimonabant vs. –0.3% with placebo (P=0.0002). Decrease in body weight from baseline was –6.7 kg with rimonabant and –2.8 kg with placebo (P<0.0001). Rimonabant reduced waist circumference (–6 vs. –2 cm, P<0.0001), fasting plasma level of glucose (–0.9 vs. –0.1 mmol/l, P=0.0012), that of triglycerides (–16.3 vs. +4.4%, P=0.0031) and increased plasma level of HDL cholesterol (+10.1 vs. +3.2%, P<0.0001). Adverse events occurred more frequently with rimonabant vs. placebo: dizziness (10.9 vs. 2.1%), nausea (8.7 vs. 3.6%), anxiety (5.8 vs. 3.6%), depressed mood (5.8 vs. 0.7%) and paraesthesia (2.9 vs. 1.4%) [44].

The ARPEGGIO Study

The ARPEGGIO Study was a double-blind, randomised, parallel-group, fixed-dose, two-arm controlled trial, a part of the phase III/b programme, to study rimonabant (20 mg daily) vs. control in the management of type 2 diabetes and cardiovascular disease. It was the first trial of rimonabant in 368 insulin-treated patients with type-2 diabetes (HbA_{1c} ≥7%), not appropriately controlled with insulin therapy (daily insulin dose greater than or equal to 30 U/day for at least 4 weeks), in addition to diet and exercise measures, performed in 12 countries, 60 centres. The primary objective of the study was to assess the effect of rimonabant 20 mg/day on HbA_{1c} over a period of 48 weeks. Other efficacy parameters were body weight, waist circumference, serum lipids, data for glycaemic control, and adverse event data.

In addition to the significant improvement of HbA_{1c}, when added to insulin for the treatment of type-2 diabetes rimonabant 20 mg/day tripled the number of diabetic patients reaching the 7% HbA_{1c} level (6.75% of patients for control group, and 18.4% for rimonabant group, P=0.0012). It also significantly (P=0.0193) decreased fasting plasma glucose, with a mean treatment difference of –0.88 mmol/l, a result consistent with the HbA_{1c} reduction. Rimonabant significantly decreased body weight over placebo, resulting in a mean treatment difference of –2.56 kg.

Fewer patients in the rimonabant group compared with the placebo group experienced serious treatment-emergent adverse events (16.8 vs. 19.3%, respectively). However, anxiety was reported in 5% of the patients in the control arm vs. 14% on rimonabant 20 mg; depression (including depressed mood) was 7.5% in the control group vs. 14% in the rimonabant group. It is important to note that most of the patients had a medical history of depression. Similar numbers of severe hypoglycaemia were reported with rimonabant 20 mg/day and control (8 and 7 cases, respectively) [45].

The STRADIVARIUS Trial

STRADIVARIUS was a multinational trial that involved 839 patients who had abdominal obesity, defined as a waist circumference of more than 102 cm for men or more than 88 cm for women, and who required coronary angiography for a clinical indication. To be eligible, patients had to have two additional risk factors of the metabolic syndrome or be a current smoker. The patients were randomly assigned to treatment with either rimonabant, 20 mg daily (422 patients) or placebo (417 patients). Both percent atheroma volume (PAV) and total atheroma volume (TAV) were determined by intravascular ultrasound technique (IVUS) on all patients at the beginning of the study and again at 18 months on 676 patients who completed the trial, regardless of whether they were still taking the study drug (PAV represents the percent of the external elastic membrane area occupied by the atheroma, whereas TAV is the absolute change in the sum of atheroma areas). In addition, changes over the course of the study in the patients' weight and waist circumference and in several biochemical parameters, including HDL, triglyceride, and CRP levels and in the level of haemoglobin A1c (HbA_{1c}) in patients with diabetes, were also documented.

At 18 months, in rimonabant-treated patients body weight decreased by 4.3 kg, compared with 0.5 kg for those in the placebo group (P<0.001). There was also a significant difference in the decrease in waist circumference in the two groups (4.5 cm in the rimonabant arm vs. 1.0 cm in the placebo arm, P<0.001). Although there was a tendency favouring rimonabant treatment, the primary end point did not show a significant difference: PAV increased by 0.25% (–0.04 to 0.54) in the rimonabant arm and by 0.51% (0.22 to 0.80) in the placebo arm (P=0.22). However, there was a significant (P=0.03) difference between the two groups as the TAV decreased by 2.2 mm^3 (–4.09 to –0.24) in the rimonabant arm and increased by 0.88 mm^3 (–1.03 to 2.79) in the placebo arm. In the subgroup analyses, rimonabant also significantly reduced PAV in patients who were not taking statins (by 1.31% compared with placebo) and in those with high baseline triglyceride levels (≥140 mg/ml), among whom a decrease in PAV of 0.77% vs. placebo was observed. Rimonabant increased the HDL level by 22.4% (vs. 6.9% in the placebo arm), and reduced the triglyceride level by 20.5% (vs. 6.2%), and the CRP level by 50.3% (vs. 30.9%) For all differences P<0.001. Among patients with diabetes, the HbA_{1c} level decreased by 0.11% in the rimonabant arm and increased by 0.40% in the placebo arm (P<0.001).

Higher frequency of psychiatric adverse events in the rimonabant arm (43.4 vs. 28.4%, P<0.001) was noted. Anxiety (rimonabant by 18.0% vs. placebo by 11.8%, P=0.01) and depression (rimonabant by 16.8% vs. placebo by 11.3%, P=0.02) significantly increased. However, it is important to note that about 25% of the patients in the study had a history of psychiatric disease at the start of the trial [46].

The ADAGIO-LIPIDS Trial

ADAGIO-LIPIDS was a phase 3, randomized, double-blind, placebo-controlled multicentre study to determine the net effect of rimonabant on HDL cholesterol and triglyceride levels, and on the cardiometabolic profile of weight-stable overweight/obese patients with atherogenic dyslipidaemia. The CT analysis was conducted to measure how much subcutaneous and visceral fat was lost on rimonabant as well as to determine whether rimonabant could reduce liver fat. In 53 sites in 14 countries 404 patients were randomized to rimonabant 20 mg/day (297 completed) and another 395 patients to placebo (294 completed). Patients in both the treatment and placebo arms altered their diets, reduced daily caloric intake by 600 kcal after randomization to treatment and were followed for 12 months. Thus both groups of patients reduced body weight and waist circumference, and increased HDL cholesterol levels, before active treatment began.

At one year as compared with placebo, rimonabant significantly (P<0.0001) increased HDL cholesterol levels by 8.7% (vs. 1.8% in placebo), and reduced triglycerides by 19.5% (vs. 2.7% in placebo). Changes in apolipoprotein levels also improved significantly with rimonabant, as did HDL and LDL cholesterol particle size. Blood pressure was reduced significantly (P<0.0001) by 3/3 mm Hg (systolic/diastolic BP, respectively) with rimonabant, as compared with placebo (BP did not change). Levels of CRP were also reduced with rimonabant by 10.4% (vs. 7.8% in placebo), and those of adiponectin were increased by 23.0% (vs. 5.1% in placebo). Body weight was decreased in the rimonabant-treated group by 5.8 kg (vs. 2.2 kg in placebo), and waist circumference by 6.2 cm (vs. 3.3 in placebo).

In the CT analysis as compared with placebo, rimonabant treatment significantly reduced total adipose tissue by 12.2% (vs. 5.2% in placebo), visceral fat by 16.0% (vs. 5.9 in placebo), and subcutaneous fat by 9.7% (vs. 4.7% in placebo) at 12 months. The fatty liver index, a measure of hepatic steatosis, was also improved significantly (P<0.0017) with rimonabant by 0.16 (vs. 0.05 in placebo).

ADAGIO-LIPIDS included patients with no history of psychiatric and/or depressive illness, and as a result, discontinuation of therapy due to adverse events was significantly less than has been reported in other studies. Because of treatment-emergent

adverse events only 57 patients discontinued the trial in the rimonabant-treated patients and 40 patients in the placebo group [47].

Who could/should be treated by the CB_1 antagonist rimonabant? The most important indications for this treatment were elegantly summarized by Di Marzo [48] as follows:

1) patients with marked intra-abdominal obesity, high triglyceride levels, low HDL cholesterol levels and low insulin sensitivity, because the greatest reduction in cardiometabolic risk factors, and probably atherosclerosis, is likely to be observed in these individuals;
2) patients who are not prone to have or who have had no history of depression;
3) regarding the association of depression with extreme obesity, rimonabant therapy might be safer and more valuable in patients with a BMI of 27-33 kg/m^2, dyslipidaemia, pre-diabetes, and a large waist circumference, than in very obese individuals.

Unfortunately, ongoing trials aiming to assess the efficacy of prolonged (≥2 years) treatment with rimonabant at reducing carotid intima-media thickness (the AUDITOR trial), the likelihood of developing type 2 diabetes (the RAPSODI trial), and the long-term risk of cardiovascular events (the CRESCENDO trial) have been stopped. These studies would have been able to define more accurately the proper patient groups in which CB_1 antagonists may improve the cardiometabolic risk.

Taking into account that rimonabant and taranabant easily cross the blood-brain barrier, most psychiatric side effects of these drugs stem from their effects on CB_1 receptors in the CNS; therefore drugs acting only at CB_1 receptors outside the CNS might have important clinical value in reducing cardiometabolic risk. There is growing evidence for CB_1 receptors in peripheral tissues modulating pain sensitivity and obesity-related hormonal and metabolic abnormalities (see reviews: [49-51]). It has recently been reported that LH-21, a CB_1 antagonist with limited brain penetration, reduced food intake but did not affect dyslipidaemia or hepatic steatosis in obese Zucker rats, but the anti-obesity effect of this compound may not be related to CB_1 receptor blockade [52, 53]. Two small molecules with high affinity for the CB_1 receptor (<30 nM), and selectivity vs. CB_2 receptors, JD-2114 and JD-5006, have also been synthesised and found to equally reduce body weight and improve associated lipid and glycaemic risk factors as did rimonabant in a diet-induced model of obesity in mice [54].

Further studies are needed to shed light on the future of CB1 receptor antagonism in clinical practice.

References

1. Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc 1964; 86: 1646-7.
2. Matsuda LA, Lolait SJ, Browstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature (London) 1990; 346: 561-64.
3. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature (London) 1993; 365: 61-5.
4. Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 2006; 58: 389-462.
5. Lauckner JE, Hille B, Mackie K. The cannabinoid agonist WIN55212-2 increases intracellular calcium via CB1 receptor coupling to Gq/11 G proteins. Proc Natl Acad Sci USA 2005; 102: 19144-9.
6. Mackie K, Lai Y, Westenbroek R, Mitchell R. Cannabinoids activate an inwardly rectifying potassium conductance and inhibit Q-type calcium currents in AtT20 cells transfected with rat brain cannabinoid receptor. J Neurosci 1995; 15: 6552-61.
7. Mukhopadhyay S, Howlet AC. Chemically distinct ligands promote differential CB1 cannabinoid receptor-Gi protein interaction. Mol Pharmacol 2005; 67: 2016-24.
8. Járai Z, Wagner JA, Varga K, et al. Cannabinoid-induced mesenteric vasodilation through an endothelial site distinct from CB1 or CB2 receptors. Proc Natl Acad Sci USA 1999; 96: 14136-41.
9. Hájos N, Ledent C, Freund TF. Novel cannabinoid-sensitive receptor mediates inhibiton of glutamatergic synaptic transmission in the hippocampus. Neuroscience 2001; 106: 1-4.
10. Lauckner JE, Jensen JB, Chen HY, Lu HC, Hille B, Mackie K. GPR55 is a cannabinoid receptorthat increases intracellular calcium and inhibits M current. Proc Natl Acad Sci USA 2008; 105: 2699-704.
11. Rinaldi-Carmona M, Barth F, Héaulme M, et al. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 1994; 350: 240-4.
12. Rinaldi-Carmona M, Barth F, Millan J, et al. SR144528, the first potent and selective antagonist of the CB2 cannabinoid receptor. J Pharmacol Exp Ther 1998; 284: 644-50.
13. Ledent C, Valverde O, Cossu G, et al. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. Science 1999; 283: 401-4.
14. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992; 258: 1946-9.
15. Mechoulam R, Ben-Shabat S, Hanus L, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol 1995; 50: 83-90.
16. Sugiura T, Kondo S, Sukagawa A, et al. 2-arachidonoyl-glycerol: a possible endogenous cannabinoid receptor ligand in the brain. Biochem Biophys Res Commun 1995; 215: 89-97.
17. Vogel Z, Barg J, Levy R, Saya D, Helman E, Mechoulam R. Anandamide, a brain endogenous compound, interacts specifically with cannabinoid receptors and inhibits adenylate cyclase. J Neurochem 1993; 61: 352-5.
18. Felder CC, Briley EM, Axelrod J, Simpson JT, Mackie K, Devane WA. Anandamide, an endogenous cannabimimetic eicosanoid, binds to the cloned cannabinoid receptor and stimulates receptor mediated

signal transduction. Proc Natl Acad Sci USA 1993; 90: 7656-60.
19. Di Marzo V, Fontana A, Cadas H, et al. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. Nature (London) 1994; 372: 686-91.
20. Liu J, Wang L, Harvey-White J, et al. Multiple pathways involved in the biosynthesis of anandamide. Neuropharmacology 2008; 54: 1-7.
21. McKinney MK, Cravatt BF. Structure and function of fatty acid amid hydrolase. Annu Rev Biochem 2005; 74: 411-34.
22. Dinh TP, Carpenter D, Leslie FM, et al. Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc Natl Acad Sci USA 2002; 99: 10819-24.
23. Di Marzo V, Goparaju SK, Wang L, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature (London) 2001; 410: 822-25.
24. Jo YH, Chen YJ, Chua SC Jr, Talmage DA, Role LW. Integration of endocannabinoid and leptin signaling in an appetite-related neural circuit. Neuron 2005; 48: 1055-66.
25. Ravinet Trillou C, Arnone M, Delgorge C, et al. Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced obese mice. Am J Physiol Regul Integr Comp Physiol 2003; 284: R345-53.
26. Kunos G, Osei-Hyiaman D. Endocannabinoid involvement in obesity and hepatic steatosis. Am J Physiol Gastrointest Liver Physiol 2008; 294: 1101-04.
27. Pagano C, Pilon C, Calcagno A, et al. The endogenous cannabinoid system stimulates glucose uptake in human fat cells via phosphatidylinositol 3-kinase and calcium-dependent mechanisms. J Clin Endocrinol Metab 2007; 92: 4810-9.
28. Cota D, Marsicano G, Tschöp M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. J Clin Invest 2003; 112: 423-31.
29. Bensaid M, Gary-Bobo M, Esclangon A, et al. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. Mol Pharmacol 2003; 63: 908-14.
30. Gary-Bobo M, Elachouri G, Gallas JF, et al. Rimonabant reduces obesity associatedhepatic steatosis and feature of metabolic syndrome in obese Zucker fa/far rats. Hepatology 2007; 46: 122-9.
31. Osei-Hyiaman D, Liu J, Zhou L, et al. Hepatic CB1 receptor involvement in diet-induced steatosis, altered lipid profile, and insulin and leptin resistance. J Clin Invest 2008.
32. Liu YL, Connoley IP, Wilson CA, Stock MJ. Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lep (ob)/Lap (ob) mice. Int J Obes 2005; 29: 183-7.
33. Sattar N, McConnachie A, Shaper AG, et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet 2008; 371: 1927-35.
34. Kahn R. Metabolic syndrome – what is the clinical usefulness? Lancet 2008; 371: 1892-3.
35. Heisler M, Hogan MM, Hofer TP, et al. When more is not better: treatment intensification among hypertensive patients with poor medication adherence [Abstract]. Circulation 2008; 117: 2884-92.
36. Kerr EA, Zikmund-Fisher BJ, Klamerus ML, Subramanian U, Hogan MM, Hofer TP. The role of clinical uncertainty in treatment decisions for diabetic patients with uncontrolled blood pressure [Abstract]. Ann Intern Med 2008; 148: 717-27.
37. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J; RIO-North America Study Group. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients. RIO-North America: A randomized controlled trial. JAMA 2006; 295: 761-75.
38. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rössner S; RIO-Europe Study Group. 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: 1389-97.
39. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal L; RIO-Diabetes Study Group. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet 2006; 368: 1660-72.
40. Després JP, Golay A, Sjöström L; Rimonabant in Obesity-Lipids Study Group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 2005; 353: 2121-34.
41. Curioni C, André C. Rimonabant for overweight or obesity. Cochrane Database Syst Rev 2006; (4): CD006162. Available at: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD006162/frame.html.
42. Van Gaal L, 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 (Suppl. 2): S229-40.
43. Ruilope LM, Després JP, Scheen A, et al. Effect of rimonabant on blood pressure in overweight/obese patients with/without co-morbidities: analysis of pooled RIO study results. J Hypertens 2008; 26: 357-67.
44. Rosenstock J, Hollander P, Chevalier S, Iranmanesh A; SERENADE study group. SERENADE: the Study Evaluating Rimonabant Efficacy in Drug-naive Diabetic Patients: effects of monotherapy with rimonabant, the first selective CB1 receptor antagonist, on glycemic control, body weight, and lipid profile in drug-naive type 2 diabetes. Diabetes Care 2008; 31: 2169-76.
45. Hollander P; ARPEGGIO Study. Presented on June 10, at the 68th Scientific Sessions of the American Diabetes Association 2008, in San Francisco.
46. Nissen SE, Nicholls SJ, Wolski K, et al; STRADIVARIUS Investigators. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease. The STRADIVARIUS randomized controlled trial. JAMA 2008; 299: 1547-60.
47. Després JP, Ross R. Presented at the 77th European Atherosclerosis Society Congress, 2008 in Istanbul. Sanofi Aventis (online 5 May 2008): Imaging results from the ADAGIO-Lipids reveal that effects of rimonabant on cardiometabolic risk profile include loss of visceral fat and mobilization of liver fat. Available at: http://www.sanofi-aventis.se/live/se/sv/ layout. jsp?cnt=52DC240C-CD09-4B62-87DCC3FDD0B8AA43, (accessed 3 July 2008).
48. Di Marzo V. Play an ADAGIO with a STRADIVARIUS: the right patient for CB1 receptor antagonists? Nat Clin Pract Cardiovasc Med 2008; 5: 610-2.
49. Kunos G, Osei-Hyiaman D, Bátkai S, Sharkey KA, Makriyannis A. Should peripheral CB1 cannabinoid receptors be selectively targeted for therapeutic gain? Trends Pharmacol Sci 2009; 30: 1-7.

50. Kunos G, Osei-Hyiaman D, Liu J, Godlewski G, Bátkai S. Endocannabinoids and the control of energy homeostasis. J Biol Chem 2008; 283: 33021-5.
51. Nogueiras R, Veyrat-Durebex C, Suchanek PM, et al. Peripheral, but not central. CB1 antagonism provides food intake independent metabolic benefits in diet-induced obese rats. Diabetes 2008; 57: 2977-91.
52. Pavón FJ, Serrano A, Pérez-Valero V, et al. Central versus peripheral antagonism of cannabinoid CB1 receptor in obesity: effects of LH-21, a peripherally acting neutral cannabinoid receptor antagonist, in Zucker rats. J Neuroendocrinol 2008; 20 (Suppl 1): 116-23.
53. Chen RZ, Frassetto A, Lao JZ, et al. Pharmacological evaluation of LH-21, a newly discovered molecule that binds to cannabinoid CB1 receptor. Eur J Pharmacol 2008; 584: 338-42.
54. McElroy J, Sieracki K, Chorvat R. Non-brain-penetrant CB1 receptor antagonists as a novel treatment of obesity and related metabolic disorders. Obesity 2008; 16 (Suppl. 1): S47.