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NEW THERAPIES FOR DIABETES

The endocannabinoid system,

a promising target for the management of type 2 diabetes

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SUMMARY (Max 250 words : 250)

Type 2 diabetes is closely related to abdominal obesity and is generally associated with other cardiometabolic risk factors, resulting in a high incidence of cardiovascular complications. Several animal and human observations suggest that the endocannabinoid (EC) system is overactivated in presence of abdominal obesity and/or diabetes, and contributes to disturbances of energy balance and metabolism. Not only it regulates the intake of nutrients through central mechanisms located within the hypothalamus and limbic area, but it also intervenes in transport, metabolism and deposit of the nutrients in the digestive tract, liver, adipose tissue, skeletal muscle, and possibly pancreas. Activation of both central and peripheral CB1 receptors promotes weight gain and associated metabolic changes. Conversely, rimonabant, the first selective CB_1 receptor antagonist in clinical use, has been shown to reduce body weight, waist circumference, triglycerides, blood pressure, insulin resistance and C-reactive protein levels, and to increase HDL cholesterol and adiponectin concentrations in both non-diabetic and diabetic overweight/obese patients. In addition, a 0.5-0.7% reduction in glycated hemoglobin (HbA1c) levels was observed in metformin- or sulfonylurea-treated patients with type 2 diabetes and in drug-naïve diabetic patients. Almost half of metabolic changes occurred beyond weight loss, in agreement with direct peripheral effects. Rimonabant was generally well-tolerated, but with a slightly higher incidence of depressed mood disorders, anxiety, nausea and dizziness compared to placebo. New trials are supposed to confirm the potential role of rimonabant (and other CB1 neutral antagonists or inverse agonists) in overweight/obese patients with type 2 diabetes and high risk cardiovascular disease.

Key-words : Endocannabinoid system – Cardiometabolic risk - CB1 receptor - Obesity - Rimonabant - Type 2 diabetes

Introduction

Over the last two decades a new biochemical/physiological system, known as the endocannabinoid (EC) system, was discovered [1,2]. There is now considerable evidence that the EC system plays a significant role in appetite drive and associated behaviors, but also in endocrine and metabolic regulation and energy balance [3]. Indeed, cannabinoid (CB) receptors, especially CB1 receptors, participate in the physiological modulation of many central and peripheral functions [3]. The tremendous increase in the understanding of the molecular basis of CB activity [4-6] has encouraged many pharmaceutical companies to develop synthetic CB analogues and antagonists, leading to an explosion of basic research and clinical trials [7-11]. For instance, it is reasonable to hypothesize that the attenuation of EC system overactivity would have therapeutic benefit in treating disorders that might have a component of excessive appetite drive, such as obesity and related disturbances [9,11-16]. Interestingly, whereas antagonism of CB1 receptors acutely reduces food intake, the long-term effects on weight reduction and metabolic regulation rather appear to be mediated by stimulation of energy expenditure and by peripheral effects related to adipose tissue, liver, skeletal muscle and pancreas physiology [3,17]. Such observations extend the potential use of CB1 receptor antagonists or inverse agonists, such as rimonabant (SR-141716A) and taranabant (MK-0364), for the management of abdominal obesity associated with multiple cardiometabolic risk factors, especially type 2 diabetes [18-23].

The natural history of type 2 diabetes includes initial overweight and progressive weight gain (especially increased visceral adipose tissue), progressive hyperglycemia (related to B-cell failure), insulin resistance, frequent association with other cardiovascular risk factors such as atherogenic dyslipidemia (low high density lipoprotein-cholesterol or HDL-C, high triglycerides or TG), elevated blood pressure and silent inflammation (elevated C-reactive protein or high sensitive CRP), accelerated atherosclerosis, and finally concomitant cardiometabolic disease, which typically manifests as cardiovascular disease (CVD), coronary heart disease (CHD), cerebrovascular disease and/or peripheral arterial disease [24,25]. Being overweight or obese, abdominally obese in particular, markedly increases the risk of type 2 diabetes and CVD [26-29]. The treatment of multiple cardiovascular and metabolic risk factors is central to the management of diabetic patients [24,25,30-34], and the importance of weight management is well recognized

in type 2 diabetes [35-38]. Yet individuals with type 2 diabetes often have more difficulty in losing weight and experience weight gain associated with most anti-diabetic medications [30,38]: the most plausible explanation is an increased fuel efficiency caused by the improvement in the glycemic control [39]. In addition to weight gain, adherence to drug regimens characterized by polypharmacy tends to decrease, and non-adherence to therapy undoubtedly contributes to therapeutic failure. These factors invite the investigation of new therapies that maximize CVD risk reduction with minimal intervention, possibly targeting abdominal obesity [18,22].

Considering that various organs with a key-role in diabetes-related hyperglycemia contain both ECs and CB1 receptors, the role of EC system and its therapeutic modulation deserve much attention in the pathophysiology and management of type 2 diabetes, respectively [21,23]. The aims of the present review are 1) to summarize the current knowledge of the EC system, especially the recently discovered numerous peripheral effects of ECs and the consequences of the blockade of CB1 receptors on energy control and metabolism regulation; 2) to analyze the rationale for use of CB1 receptor antagonists (or inverse agonists) in the management of overweight/obese patients with type 2 diabetes and other cardiometabolic risk factors; 3) to briefly describe the results obtained in randomized controlled clinical trials with rimonabant, a selective CB1 receptor antagonist, in non diabetic overweight/obese individuals and more particularly in patients with type 2 diabetes; 4) to succinctly present the ongoing trials with rimonabant and other CB1 receptor neutral antagonists or inverse agonists; and 5) finally to describe the benefit-risk profile of rimonabant and provide advice to target the right patient in clinical practice.

1. Brief description of the endocannabinoid system and CB1 receptor pharmacological modulation

a. The endocannabinoid system

The term “endocannabinoid” was coined in the mid 1990s after the discovery of the membrane receptors of the delta9-tetrahydrocannabinol and its endogenous ligands. Today it describes a complex signaling system comprising CB receptors, endogenous ligands, and enzymes for the synthesis and degradation of ligands (figure 1) [6].

The EC system has first emerged as a major neuromodulatory system in the brain [1,2], where ECs act as retrograde neurotransmitters (or messengers) that inhibit synaptic activity [4,5]. More recently, the EC system has also been shown to be an intercellular signaling system that plays an important role in various peripheral organs, especially those controlling energy metabolism [3]. Although ECs influence numerous behaviors, in general the net effect of ECs at diverse sites in the brain and throughout the body is anabolic, facilitating increased energy intake, decreased energy expenditure, and increased accumulation of body fat [3,20,40]. Because of its "exostatic" role [41] in our environmental conditions the activation of EC system (via CB1 receptors) leads to overeating and orients metabolism towards an excessive storage of energy resources. Furthermore, since the system is controlled by a feed-forward mechanism, during obesity it enters a pathophysiological loop that entertains the maintenance or even the aggravation of overweight [41].

Two major endogenous endocannabinoids (ECs), anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), have been identified that are derived from membrane phospholipids and triglycerides, respectively [42]. One distinctive feature of ECs is "use-dependent" synthesis. Unlike neurotransmitter molecules that are typically held in vesicles before synaptic release, ECs are synthesized on demand in response to acute stimulation within the plasma membrane [3,5,7]. This response is mediated through increased intracellular calcium concentrations. The enzymes most likely responsible for AEA and 2-AG biosynthesis have been cloned. Once released, ECs travel in a retrograde direction and transiently suppress presynaptic neurotransmitter release through binding to and functionally activating specific CB receptors. Their ability to modulate synaptic efficacy has a wide range of functional consequences and their mostly inhibitory signaling provides unique therapeutic possibilities [5,11].

Two CB receptors have been identified and molecularly characterized so far, namely CB1 and CB2 receptors [43,44]. The ubiquitous CB1 receptors are found in numerous organs involved in the regulation of energy homeostasis (see below) [3]. CB2 receptors are present almost exclusively in immune and blood cells, although some CB2 receptors have been recently described in other organs (see below). ECs are rapidly removed from the extracellular space by selective uptake into the cells and intracellular enzymatic hydrolysis. Two enzymes have been

shown to play a major role in EC degradation, the fatty acid amide hydroxylase (FAAH) and the monoacylglycerol lipase (MAGL) (figure 1) [42,45].

Mounting evidence suggests that the EC system is involved in the physiological regulation of numerous functions, many of which relate to stress-recovery systems and to the maintenance of energy balance [41]. In particular, EC system is regarded as an integrated physiological system modulating nutrient intake, transport, metabolism and storage, whose dysfunction is associated with abdominal adiposity and its associated co-morbidities [3,15,41,42]. In principle, EC system overactivity may result from increased EC synthesis, CB receptor overexpression and/or decreased EC degradation. Conversely, pharmacological modulation to correct overactivity of EC system may theoretically involve reduction of EC production, blockade of EC transport, blockade of CB1 (or CB2) receptors and/or enhancement of EC degradation [11]. As defect in ECs degradation may play a role in EC system overactivity, FAAH might represent a promising target for pharmacotherapeutic modulation [11]. However, while pharmacological agents that inhibit the activity of FAAH are still available, agents that stimulate FAAH are not in development yet. Thus EC system represents a major challenge both in our understanding of the complexity of signaling and in attempting to design drugs with selectivity of action. It does also provide an opportunity to develop therapeutic agents. Today we have drugs that bind to the CB1 receptor as agonists or antagonists, drugs that block the EC transport and drugs that inhibit the activity of FAAH. Considering the complexity and the ubiquity of the EC system [6], CB1 antagonism strategy will lead to drugs probably not with magic bullet-like specificity but more likely with multiple actions targeting different facets of the system [5]. This may be a great opportunity in the management of multifaceted diseases such as obesity and the metabolic syndrome [16] or type 2 diabetes [21,23].

b. The CB1 receptors

CB1 receptors, as CB2 receptors, are 7-transmembrane, G-protein-coupled receptors, similar to receptors for many hormones and neurotransmitters [44]. CB1 receptor and tissue concentrations of ECs sufficient to activate them are more widely distributed than originally believed. They are present in all brain and peripheral organs involved in the control of energy

homeostasis. In the brain, studies have established that ECs and CB1 receptors mediate food intake both in the hypothalamus, which control energy homeostasis, and in the limbic system, which control the pleasure aspects of eating [13,41,46].

The demonstration of the expression of CB1 receptors in adipocytes and the ability of a CB1 receptor antagonist (rimonabant) to block lipogenesis stimulated by ECs represented a first important step forward in understanding the peripheral mechanisms of action of the EC system in regulating metabolic processes [17,47]. These CB1 receptors are also found in the gut [48], liver [49], skeletal muscle [50] and pancreas [51,52], all organs playing a key-role in the pathophysiology of type 2 diabetes (see below) [21,23]. Through CB1 receptors expressed in these peripheral tissues, the EC stimulation promotes lipogenesis and fat accumulation, increases insulin resistance, induces glucose intolerance, and diminishes thermogenesis [15,20,21,41].

c. The CB1 receptor antagonists

Pharmacological investigations have placed emphasis on the generation of substances acting as specific agonists or antagonists of CB receptors [8,16,43,53]. There are different possible mechanisms by which CB1 receptor antagonists produce their effects on the CB1 receptor. The ligands can be competitive antagonists of CB1 receptor activation by endogenously released ECs (neutral antagonists), or they can act as inverse agonists and modulate constitutive CB1 receptor activity by shifting it from an active “on” to an inactive “off” state [9,54,55]. Like an antagonist, inverse agonists block receptor binding and activation by a competitive agonist, but in addition, they also inhibit intrinsic or spontaneous receptor signaling [54]. The result is an effect opposite to that produced by a given agonist and is termed inverse agonism. Whether the physiological and behavioral effects of CB1 receptor inverse agonists result from the ability of these compounds to inhibit intrinsic receptor activity or from the pharmacological blockade of endogenous EC signaling or both is not known [54]. Indeed, rimonabant, the most widely

investigated compound, appears to act both as a CB1 receptor antagonist and an CB1 receptor inverse agonist [16,54]. The observation that a neutral, high-affinity, CB1 receptor with no intrinsic activity such as AM4113 dose-dependently reduced food intake and body weight in rats, as shown with inverse agonists, supports the view that the EC system plays a physiological role in energy balance [56]. It is noteworthy that such a neutral antagonist is substantially less proemetic than a CB1 receptor inverse agonist like AM251 [56,57]. Finally, because CB1 receptors are G protein-coupled receptors, one could assume that basal G protein activity may also influence CB1 receptor activity and the metabolic functions of ECs [11]. Therefore, factors which could affect G protein activity may be taken into account for the CB1 receptor antagonist therapies, although experimental data with a specific interest for this possible effect are presently lacking.

Among the increasing number of substances sharing CB1 receptor antagonistic properties, the diarylpyrazole derivative SR141716A (rimonabant) was the first selective CB1 receptor antagonist reported [58,59] and extensively investigated not only in various sophisticated research in animals but only in large clinical trials in humans [60-64]. It is also the only one already commercialized in many countries (see below) [65].

Rimonabant successful development encouraged searching for selective CB1 receptor ligands as new chemical entities with similar or better pharmacological and safety profiles as compared to rimonabant [16,56,57,66-69]. Biosiosteric replacements and substituent modifications of the rimonabant pyrazole pharmacophore as well as de novo and high-throughout screening approaches have indeed generated many novel CB1 receptor ligands acting as neutral antagonists or inverse agonists. The CB1 receptor modulators known so far are diarylpyrazoles, or aminoalkylindoles, or triazole derivatives. Some of these compounds have been identified as being actively pursued in the biopharmaceutical industry as leads for the pharmacotherapy of obesity and related metabolic disorders, including type 2 diabetes (table 1) [16]. In general, such lead selective CB1 receptor antagonists for weight-management have

demonstrated acute preclinical activity in reducing food intake and body weight, and longer-term efficacy with chronic feeding in non-obese rodents and standard dietary and genetic obesity models [70-77]. Measurements of energy expenditure, adipose tissue mass and distribution and metabolic parameters (e.g., plasma glucose and insulin levels, lipids) have also been routine components of the lead evaluation process. However, at present, little is known about these CB1 receptor antagonists or inverse agonists, as compared to the huge amount of experimental data already available for rimonabant. Whether these new CB1 receptor antagonists or inverse agonists will have advantage over rimonabant remains an open question [78], although recent data suggested that some of them may be associated with less proemetic effects in animals [56,57,69].

An original brain imaging study used [18F]MK-9470 as a selective, high-affinity, inverse agonist for the CB1 receptor [79]. Autoradiographic studies in rhesus monkey brain showed high specific binding in the cerebral cortex, cerebellum, caudate/putamen, globus pallidus, substantia nigra, and hippocampus. Positron emission tomography (PET) imaging studies in rhesus monkeys showed high brain uptake and a distribution pattern generally consistent with that seen in the autoradiographic studies. Baseline PET imaging studies in human research subject demonstrated behaviour of [18F]MK-9470 very similar to that seen in monkeys. In addition, proof of concept studies in healthy young male human subjects showed that MK-0364, a CB1 receptor inverse agonist currently evaluated in clinical trials in obese or diabetic individuals, produced a dose-related reduction in [18F]MK-9470 binding reflecting CB1 receptor occupancy by the drug. Thus, this sophisticated technique may allow demonstration of target engagement and non-invasive dose-occupancy studies to aid in dose selection for clinical trials of CB1 receptor inverse agonists [79].

2. Experimental data on EC system, CB1 receptors, energy control and metabolism (Figure 2 and Figure 3)

a. Animal and in vitro experiments

- EC system in the brain

Exogenous CBs and ECs increase food intake and promote weight gain in rodents through activation of central CB1 receptors [3,13,15,41]. Furthermore, despite the fact that, in animals with a well balanced energy homeostasis, EC levels in the hypothalamus and limbic forebrain are elevated during food deprivation and depressed during food consumption, recent evidence suggests that the ECS, and in particular the levels of either ECs or CB1 receptors or both, become permanently up-regulated in several organs and tissues of obese animals [3,13]. ECs are part of the leptin-regulated neural activity involved in appetite regulation [80,81]. One of the sites of the orexigenic action of ECs involves activation of CB1 receptors in the lateral hypothalamus, from which neurons involved in mediating food reward project into the limbic system [41]. Consistent with the effects of ECs on feeding behavior are the results of studies with CB1 knockout mice with respect to body weight changes. CB1-/- mice are lean and resistant to diet-induced obesity, with no deterioration of insulin sensitivity [3,82]. Similar to genetic inactivation of CB1 receptors, pharmacological CB1 antagonism with rimonabant reduced food intake and body weight [80]. Pair-feeding experiments, however, revealed that the reduced food intake in rimonabant-treated mice was transient and not sufficient to reduce body weight in untreated obese mice [17]. These surprising findings suggest that body weight reduction with CB1 antagonism is only partially explained by a reduction in energy intake and that energy expenditure may also increase. Similar observations were reported with other CB1 receptor antagonists, which were shown to affect primarily metabolic parameters independent of reduced food intake in Wistar rats [73]. All of these observations have contributed to the hypothesis that peripheral ECs, and therefore CB1-receptor antagonism in peripheral organs, modulate metabolic regulation, independent of food intake [3,40].

- EC system in the adipose tissue

White adipose tissue is involved in lipid synthesis, storage, and release depending on nutritional status, while brown adipose tissue is responsible for energy consumption through uncoupled mitochondrial respiration. Brow adipose tissue is particularly active in rodents, but has almost completely disappeared in humans in normal circumstances. The CB1 receptor activation increased the activity of lipoprotein lipase in white adipocytes, and rimonabant

blocked this action [17]. Treatment of obese mice with CB1 receptor antagonists induced several metabolic events in adipose tissue, such as enhanced lipolysis through stimulation of enzymes involved in β-oxidation and the tricarboxylic acid cycle, increased energy expenditure through futile cycle induction, and an improvement in glucose uptake through increased expression of glucose transporter-4, a key player in glucose metabolism [84]. It was found that the adipocyte hypertrophy induced by high-fat diet was accompanied by increased CB1 receptor expression levels in white adipose tissue, and this CB1 receptor expression was directly regulated by peroxisome proliferator-activated receptors (PPAR)-delta [85]. Animal data were confirmed in humans. Human adipocytes have been identified as a new source of ECs and related compounds [86]. Furthermore, human adipose tissue is able to bind AEA and 2-AG and is endowed with the biochemical machinery to metabolize ECs [87]. Although CB2 receptor was also found in human adipocytes [88], its role in adipose tissue remains unknown.

Factors derived from white adipose tissue are believed to play a central role in the development and progression of metabolic disturbances, especially type 2 diabetes and its vascular complications [89,90]. Indeed, one of the major roles of white adipose tissue in metabolic control is the production of metabolism-related hormones such as adiponectin and leptin. Adiponectin increases insulin sensitivity, and thereby contributes to the decrease in levels of blood glucose and plasma insulin, and contributes to a reduction in vascular inflammation [91,92]. Interestingly, in humans, visceral adiposity is characterized by hypoadiponectinemia, which is related to impaired glucose tolerance and lipid disturbances [90]. The administration of rimonabant increased adiponectin expression in the cultured adipocytes of mice [17] and in Zucker (fa/fa) rats [93]. Moreover, in obese Zucker fa/fa rats, rimonabant increased the low level of adiponectin with concomitant decrease in the high level of tumour necrosis factor (TNF)-α, two adipokines that interplay in concert [94]. In a high-fat diet dog model, rimonabant induced a rapid dramatic increase in plasma adiponectin levels, whereas no significant changes were observed with placebo. More interestingly, the increase in adiponectin in the rimonabant-treated group occurred in the absence of changes in body weight or in omental fat [95]. These results suggest that CB1 antagonism can raise and sustain plasma adiponectin levels during high-fat feeding, an effect which may account for the concomitant increase in insulin sensitivity.

However, a recent study failed to show a significant relation between adipose tissue CB1 receptor gene expression and adiponectin mRNA or adiponectin secretion in human subcutaneous adipose tissue, but unfortunately no measurement could be performed in the omental adipose tissue [96].

Rimonabant was also found to inhibit the proliferation of preadipocyte cells and to increase adipocyte maturation without lipid accumulation [97]. The reduction of adipose tissue mass in rodents by rimonabant resulted from an enhanced lipolysis, an increased energy expenditure, and a tight regulation of glucose homeostasis [84]. Several findings indicate that the EC system participates locally in adipogenesis and fat accumulation, partially by accelerating the appearance and stimulating the activity of PPAR-γ [52]. These results clearly suggest the involvement of EC system in the function of white adipose tissue, although some controversial results have been recently reported [96].

- EC system in the gastrointestinal tract

In the gut there are regional variations in the levels of ECs with 2-AG being higher in the ileum than in the colon, and AEA being considerably higher in the colon than in the ileum [98]. In small intestine, AEA levels increased after starvation and returned with refeeding [99]. Peripheral administration of AEA increased short-term food intake, an effect that is blocked by vagal deafferentation, suggesting that intestinal lipid mediators such as AEA (and oleoylethanolamide) acting via the vagus nerve are important in the regulation of food intake [99]. Peripheral (but not central) administration of the CB1 receptor antagonist rimonabant was found to act synergistically with oleoylethanolamide to reduce food intake via the vagus nerve, suggesting a peripheral mechanism for CB1 receptor-dependent modulation of feeding [99]. These data indicate that food intake is in some part governed by a complex interaction of peripheral signals from the gut involving lipid and peptide signaling systems that converge at the level of the vagus nerve [98].

Following this observation, it was shown that rimonabant reduced the plasma levels of the orexigenic peptide ghrelin, but did alter neither levels of the hindgut hormone glucagon-like peptide-1 (GLP-1) nor plasma glucose concentrations [100]. The expression of CB1 receptors

was confirmed in vagal afferent neurons and the levels of expression and distribution of CB1 receptors were regulated by the state of satiety and inhibited by cholecystokinin (CCK) [101]. These results illustrate an interesting reciprocal action whereby CCK inhibits food intake, at least in part, by blocking the orexigenic actions of ECs produced in the gastrointestinal tract. Recently, it was discovered that receptors for ghrelin were present on the same population of vagal afferents as the CB1 and CCK1 receptors (as are melanin-concentrating hormone and leptin receptors) [102]. Activation of the ghrelin receptor prevented the downregulation of the CB1 (and melanin-concentrating hormone) receptors by CCK, thereby limiting the extent of its action [102]. This illustrates a new role for ghrelin in modulating the expression of receptors for other orexigens. Thus a considerable amount of evidence now suggests that the EC system may regulate food intake by also acting in the gastrointestinal tract and in the gut-brain signalling [48,98,99].

Finally, within the gastrointestinal tract, the EC system has been reported to be involved in the regulation of motility, secretion, sensation, emesis, satiety and inflammation [103]. Animal data showing that rimonabant prevented ulcer formation and inhibited increase in TNF-α levels suggested that modulation of endogenous EC system and CB1 receptors function could interfere with inflammatory gastrointestinal tract [104]. However, further efforts are required to characterize the role of the EC system on the gut-brain axis in gastrointestinal disorders [98].

- EC system in the liver

Wild-type (CB1+/+) mice on high fat diet became obese and developed a fatty liver while CB1-/- mice, although having a similar caloric intake, remained unaffected. Lipogenesis was markedly increased in wild-type mice on the high fat diet before appearance of a marked weight gain. This increment was suppressed by a pre-treatment with rimonabant. At the same time, hepatic levels of AEA were greatly elevated in mice on the high fat diet with no difference in hepatic levels of 2-AG. Higher levels of AEA may be explained by a strong reduction in FAAH activity [49]. In liver, ECs induce the expression of a cluster of genes that stimulate hepatic fat synthesis, including the lipogenic transcription factor sterol regulatory element-binding protein (SREBP)-1c and the key lipogenic enzymes acetyl coenzyme A carboxylase-1 and fatty acid

synthase. As a result, CB1 activation significantly increased fatty acid synthesis in normal mice, whereas the effect by CB1 agonist was not observed in CB1 receptor knockout mice or in normal mice treated with rimonabant [49].

The treatment with rimonabant reduced obesity-associated hepatic steatosis and features of metabolic syndrome, especially dyslipidemia, in obese Zucker fa/fa rats [94]. All together these data indicate that ECs promote lipogenesis and steatosis in the liver through CB1 receptors [105]. This also suggests that ECS activation may contribute to the pathogenesis of non-alcoholic fatty liver disease (NAFLD) or even steatohepatitis (NASH), two common features in overweight/obese patients with type 2 diabetes which are strongly associated with insulin resistance [106,107]. Furthermore, the hepatic EC system mediates both pro- and antifibrogenic effects by activating distinct signaling pathways that differentially affect proliferation and death of fibrogenic cell types [108]. In animals, the fibrotic response of liver was strongly diminished by antagonism or genetic inactivation of CB1 receptors, suggesting that CB1 receptor antagonism may represent a new strategy for the treatment of liver fibrosis [108]. This might be of interest to prevent liver fibrosis which may appear after a NASH in some obese patients, especially in presence of type 2 diabetes [106].

- EC system in the skeletal muscle

Skeletal muscle plays a major role in metabolic regulation and the insulin sensitivity of skeletal muscle is critical in the regulation of glycemic control [21]. An important target organ of CB1 receptor antagonists in Lep(ob)/Lep(ob) obese mice is the skeletal muscle. Indeed, a significant increase in glucose uptake by isolated soleus muscle and oxygen consumption was observed in obese mice when treated with rimonabant [50]. The CB1 receptor is expressed in human skeletal muscle and the EC AEA modifies the pathways that regulate fatty acid oxidation in human skeletal muscle [109]. ECs were reported to suppress fatty acid oxidation in skeletal muscle by affecting the expression of energy metabolism-regulating genes including AMP-activated protein kinases α1 and α2, pyruvate dehydrogenase kinase 4, and PPAR-γ co-activator-1α [109]. However, not all of the effects of AEA can be accounted for by blocking the CB1 receptor with a specific CB1 receptor antagonist, suggesting the presence of other receptors for

ECs in skeletal muscle. A recent study described the presence of not only CB1 receptors, but also CB2 receptors and the "non-canabinoid" transient receptor potential channel-vanilloid sub-family member 1 (TRPV1) in rodent and human skeletal muscle, and also evidenced the presence of the degrading enzyme FAAH [110]. Consequently ECs may have a complex role in skeletal muscle biology. It is not known, however, if the effect of chronic treatment with rimonabant results from a direct effect of the drug on skeletal muscle CB1 receptors or an indirect effect due to the increase in adiponectin secretion [92]. This deserves further studies as skeletal muscle is a key organ playing a major role in the insulin resistance characterizing type 2 diabetes in humans [21].

- EC system in the pancreas

Recent animal studies extended the potential role of the EC system to the endocrine pancreas [17,51,52,111-115]. CB1- and CB2 receptors as well as enzymes for EC biosynthesis and metabolism are expressed in islets of Langerhans of mice and rats and in rat insulinoma RIN-m5F B-cells, a commonly used model of pancreatic B-cells [52]. In rats, the administration of AEA and its stable analogue arachidonyl-2'-chloroethylamide resulted in glucose intolerance after a glucose load, which may be due to the reduction of glucose-dependent insulin secretion [111]. Whereas stimulation of CB1 receptors in the rat leads to glucose intolerance, activation of CB2 receptors improves glucose handling after a glucose load, and blockade of CB2 receptors counteracted this effect [111,112]. In mice, CB2 modulate calcium oscillations and insulin secretion in vitro [51]. These findings suggest a role of CB2 receptors in the control of insulin secretion in rodents.

Immunohistochemical study revealed that CB1 receptor was expressed in B-cells of mouse pancreatic islets [113]. AEA and a CB1 receptor agonist, arachidonylcyclopropylamide, inhibited glucose-induced cytosolic Ca^{2+} oscillation and consequently insulin secretion in mouse pancreatic islets. Moreover, a FAAH inhibitor, N-arachidonylglycine, modulates insulin secretion and Ca^{2+} oscillations in mouse islets and B-cells [114]. These actions are derived from glucose-induced alterations in EC production, as demonstrated in the pancreatic B-cell line RIN-

m5F. Thus, elevations of glucose concentration in the culture media are associated with a rise in the levels of both 2-AG and AEA [17,52].

Human islets of Langerhans expressed CB1 and CB2 mRNA and CB1 and CB2 proteins, and also the machinery involved in synthesis and degradation of 2-AG, the most abundant EC, levels of which were modulated by glucose [115]. Immunofluorescence revealed that CB1 receptor was densely located in glucagon-secreting A-cells and less so in insulin-secreting B-cells, whereas CB2 receptor was densely present in somatostatin-secreting D-cells, but absent in A- and B-cells. In vitro experiments revealed that CB1 receptor stimulation enhanced insulin and glucagon secretion, while CB2 receptor agonism lowered glucose-dependent insulin secretion, showing these CB receptors to be functional in humans too. Further in vivo studies will be necessary to establish the impact of CB1 receptor antagonists on human pancreatic B-cells under physiological conditions, in both normal individuals and patients with type 2 diabetes.

b. In vivo or ex vivo human data

There is increasing evidence in humans for overactivity of the EC system during conditions of unbalanced energy homeostasis, i.e. obesity (especially abdominal obesity) and diabetes, and for its causative role in these disorders [116]. Preliminary data found that circulating levels of AEA and 2-AG were significantly increased in obese compared with lean postmenopausal women [117]. Furthermore, circulating 2-AG was significantly correlated with body fat, visceral fat mass, and fasting plasma insulin concentrations, but negatively correlated to glucose infusion rate during a euglycemic hyperinsulinemic clamp in a group of 10 men and 10 women [118]. Obese subjects had a reduction in adipose tissue FAAH gene expression compared with lean individuals [96,117,118], and FAAH gene expression was negatively correlated with visceral fat mass and with circulating 2-AG [118]. Another group of researchers also showed higher levels of 2-AG in the serum and visceral, but not subcutaneous, fat of obese subjects [52]. In a further study in untreated asymptomatic men, plasma 2-AG levels correlated positively with BMI, waist girth, intra-abdominal adiposity, fasting TG and plasma insulin levels, and negatively with HDL-C and adiponectin levels [119]. Another study confirmed that the ECS is activated in obese visceral adipose tissue and that the obesity-related ECS activation is accompanied by

elevated expression of the pro-inflammatory cytokine TNF-a, which in turn stimulates ECS activation in vitro [120]. These findings show a strong association between adipose tissue inflammation and ECS activation in obesity, and indicate that a pro-inflammatory state may directly activate the ECS.

Recent data indicated a role for the local ECs in the regulation of glucose metabolism via phosphatidylinositol 3-kinase and calcium-dependent mechanisms in human adipocytes, and suggested a role in channelling excess energy fuels to adipose tissue in obese humans [121]. Interestingly, following hyperinsulinemia resulting from a euglycemic hyperinsulinemic clamp, the FAAH mRNA levels significantly increased approximately twofold in the subcutaneous abdominal adipose tissue from lean but not from obese individuals. The FAAH gene expression positively correlated with the fasting serum insulin concentration, whereas an inverse association with the whole-body glucose disposal was seen [122]. According to these data insulin may play a key-role in the obesity-linked dysregulation of the adipose EC system at the gene level.

One recent study, however, did not show a major role of human adipose tissue CB1 receptor gene in fat cell function or metabolic disease development [96]. Indeed, no association between either subcutaneous or omental adipose tissue CB1 receptor gene mRNA levels and BMI, waist circumference, plasma levels of glucose and insulin, or lipids was found. Furthermore, no relation was found between adipose tissue CB1 receptor gene expression and adiponectin mRNA, adipose tissue adiponectin secretion, or circulating adiponectin, contrasting with previous data in fa/fa rats [93]. Results from adipocyte functional studies confirmed in vivo data, as lipolysis in the subcutaneous and omental fat cells and lipogenesis in subcutaneous adipocytes were not different in subjects with either a high or a low CB1 receptor gene expression level [96]. Unfortunately, there was not enough tissue available for analysis of protein levels of CB1 receptor to confirm the mRNA data. The reason for these conflicting results is unknown and further studies are needed to better understand the role of CB1 receptor in human adipocyte function, and to verify the relationship between EC overactivity and low adiponectin levels in humans

ECs are not normally released from tissues into the bloodstream to act as hormone-like molecules. Therefore, the findings of elevated EC circulating levels suggest an upregulation of

EC production and/or a reduced EC degradation in peripheral organs during obesity and hyperglycemia and a "spill over" of ECs into the blood [116]. All together, these findings suggest that intra-abdominal fat accumulation is a critical correlate of peripheral ECS dysregulation and that the EC system may represent a primary target for the treatment of abdominal obesity and associated metabolic changes, including type 2 diabetes (figure 4) [21,23].

There is, as yet, no clear explanation for the mechanisms responsible for hyperactivation of the EC tone in obesity. Since the early 1990s, a number of genetic polymorphisms in the genes and proteins of the EC system have been characterized [123]. Several recent studies seem to point toward a possible role of genetic mutations to explain the overactivity of the EC system, although the topic remains controversial and deserves further investigation. A genetic polymorphism of one of the enzymes responsible for EC breakdown (FAAH) has been linked with overweight and obesity in both white and black subjects [124]. A mutation in FAAH was also shown to influence lipid changes after a low fat diet in obese subjects [125]. Furthermore, single nucleotide polymorphisms of the gene encoding CB1 receptor have been shown to be associated with BMI and fat distribution in two independent samples of white European adult men [126]. Another Belgian study reported that the G1422A variant of the CB1 receptor gene is associated with abdominal adiposity in adult obese men without diabetes, impaired glucose tolerance or other endocrine diseases [127]. In a small study group of obese and normal-weight Italians, homozygotes for the wild-type G-allele of the CB1 receptor seemed to be heavier than carriers of all other gentotypes; however, the analysis was not corrected for multiple testing and the data had not yet been confirmed independently [128]. In contrast, no evidence for an involvement of several variants in the CB1 receptor gene in obesity of German children and adolescents was shown in large samples comprising obesity trios and independent obesity families [129]. Thus, further genetic studies are awaited in order to better understand predisposition factors leading to EC system overactivity and perhaps target individuals with expected better therapeutic response with CB1 receptor antagonists.

3. Cardiometabolic effects of rimonabant in overweight/obese non-diabetic patients

a. RIO-EUROPE, RIO-North America and RIO-Lipids

The selective CB1 receptor blocker rimonabant has been carefully evaluated in the phase III RIO (Rimonabant In Obesity) program involving above 6,600 overweight/obese patients [61,64]. This programme comprised three large placebo-controlled randomized clinical trials (RCTs) in overweight/obese non-diabetic patients : two 2-year RCTs (RIO-Europe and RIO-North America) [130-132] and one 1-year RCT (RIO-Lipids) specifically devoted to patients with untreated dyslipidaemia [133]. These three RCTs led to remarkably consistent results (figure 5). After one year of follow up, rimonabant 20 mg has been shown to produce significant weight loss (-4.7 to -5.4 kg) and waist circumference reduction (-3.6 to -4.7 cm) as compared to placebo, when combined with diet and exercise advices. In addition, improvements in multiple cardiovascular and metabolic risk factors were noticed. In particular, consistent significant reductions in TG levels (-12.4 to -15.1 %) and increases in HDL-C levels (+7.2 to +8.9 %) were observed in overweight/obese patients treated with rimonabant 20 mg as compared to placebo [130,132]. These improvements persisted after 2 years, with placebo-subtracted differences almost similar as after 1 year for changes in body weight, waist circumference, TG and HDL-C [131,132].

These data were further confirmed in overweight/obese patients with untreated dyslipidemia and part of these metabolic improvements (especially HDL-C increment) could be attributed to a significant increase in plasma adiponectin levels with rimonabant 20 mg [133]. The levels of LDL cholesterol levels were not affected by rimonabant, but the drug was associated with a shift to a lower proportion of small dense LDL particles, the most atherogenic ones [133]. A post-hoc analysis demonstrated that the positive effects of rimonabant on atherogenic dyslipidemia (low HDL-C and high TG) were almost similar in patients receiving or not receiving a cholesterol-lowering therapy with statin [134]. A moderate reduction in systolic and diastolic blood pressure was also observed in the rimonabant group as compared to the placebo group, and such a reduction was greater and highly significant in patients with elevated blood pressure at baseline [135]. Fasting plasma insulin concentrations and HOMA (Homeostasis Model Assessment) insulin resistance index were significantly decreased in patients receiving rimonabant 20 mg compared to placebo. The prevalence of the metabolic syndrome as defined with the National

Cholesterol Educational Program - Adult Treatment Panel III (NCEP-ATP III) criteria was significantly reduced in all three trials. Finally, the levels of C-reactive protein were also diminished (-25 %) in the rimonabant-treated group of the RIO-Lipids trial [133].

To quantify to what extent the improvements in cardiometabolic risk factors are attributable to a direct effect of rimonabant, pre-specified analyses were performed using pooled data [136] from patients in RIO-Europe [130], RIO-North America [132], RIO-Lipids [133], and also RIO-Diabetes [137]. Changes from baseline in cardiometabolic variables (body weight, lipids, fasting glucose and insulin) at year 1 were analyzed by using analysis of covariance with weight loss as a covariate. Almost half (between 45% and 57%) of the overall treatment effect in year 1 on HDL-C, TG, fasting insulin and insulin resistance was due to a direct effect not attributable to weight loss. Weight-loss adjusted improvements in all factors were significantly better with rimonabant than placebo ($p<0.001$ for HDL-C and TG, $p<0.02$ for fasting insulin and insulin resistance). These results were supported by analysis using weight loss category. These findings were confirmed at year 2 in RIO-Europe [131] and RIO-North America [132]. These improvements in cardiometabolic risk factors beyond weight loss are possibly due to a direct pharmacologic effect of rimonabant in peripheral tissues, in agreement with increasing evidence from animal data (see above).

To determine whether rimonabant improves glucose tolerance in overweight/obese non-diabetic patients, data were pooled from the two studies involving oral glucose tolerance tests (OGTTs) at baseline and 1 year (RIO-Lipids and RIO-Europe) [138]. After 1 year, rimonabant 20 mg produced significantly greater reductions than placebo in plasma glucose (–0.64 vs –0.37 mmol/l, $p<0.01$) and insulin (–15.2 vs –1.8 μIU/ml, $p<0.001$) levels at 120 minutes post-OGTT. Rimonabant 20 mg also significantly reduced both glucose and insulin area under the plasma concentration–time curve (AUC) values versus placebo (both $p<0.001$). Furthermore, rimonabant 20 mg significantly improved the distribution of glucose tolerance status at 1 year in the pooled intent-to-treat population ($p<0.01$), with an increased proportion of patients who improved from impaired glucose tolerance (IGT) or diabetes (DGT) at baseline to normal glucose tolerance (NGT) at 1 year (64.9 vs 51.8 %, $p<0.05$) and a decreased proportion of patients who deteriorated from NGT to IGT or DGT (5.1 vs 9.3 %, $p<0.05$) [138]. Favorable effects on

glucose tolerance status persisted after 2 years, despite a weight stabilization from year 1 to year 2 as shown in the RIO-Europe trial [139]. At year 2, significant improvements were observed for fasting plasma glucose, plasma insulin and HOMA insulin resistance index with rimonabant 20 mg compared to placebo. Reductions in post-OGTT 0-120 min AUCs for both glucose (-46 vs -6 mmol/l/min; $p=0.002$) and insulin (-1217 vs -80 µIU/ml/min; $p<0.001$) were greater with rimonabant than with placebo. Again, more patients improved from IGT/DGT to NGT (70.2 vs 46.4%; $p<0.05$) whereas fewer patients with NGT at baseline worsened to IGT/DGT (6.0 vs 10.8%; $p=0.053$) with rimonabant than with placebo [139]. These results demonstrate that rimonabant 20 mg can reduce the progression of glucose intolerance in overweight/obese patients and suggest the potential of the CB1 receptor antagonist to prevent type 2 diabetes.

b. Rimonant in Japanese and Asian people

The results of the initial RIO program were mainly obtained in Caucasians. They were recently confirmed in an Asian population, first in a Japanese dose-response study of rimonabant in obese patients (BMI > 25 kg/m²) [140] and second in the larger RIO-ASIA trial (RIO-ASIA : ClinicalTrials.gov Identifier: NCT00325546) [141]. A dose response was observed when prescribing rimonabant 5 mg, 10 mg and 20 mg, compared to placebo, as far as reductions in body weight, waist circumference, visceral adipose tissue and triglycerides and increase of HDL-C were concerned. Improvements in cardiometabolic risk factors reported in the obese Japanese population were similar to those previously observed in the Caucasian population. In addition, this was the first study to demonstrate that rimonabant 20 mg achieves significant reduction in visceral adipose tissue in humans [140]. RIO-Asia was a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose (rimonabant 20mg), multi-national, multicentre study of weight-reducing effect and safety of rimonabant in 640 obese (BMI > 25 kg/m²) patients with or without comorbidities. The primary outcome was the effect on weight loss and weight maintenance over 9 months when prescribed with a hypocaloric diet in obese patients. As in the overall RIO program, secondary outcomes measures were effects on HDL-C, TG, fasting-insulin, fasting glucose, waist circumference, safety and tolerability. This study has been completed, but not published yet. In general, data from RIO-ASIA confirmed previous

observations of the initial RIO-program. Several other studies are ongoing in Japanese patients with dyslipidemia (VENUS) or type 2 diabetes (SOLO, SYMPHONY) (see below).

c. ADAGIO

Another large trial is completed, the ADAGIO trial (ClinicalTrials.gov identifier: NCT00239967) [142] ADAGIO was a randomized, double-blind, two-arms placebo-controlled, parallel-group, multicenter study of rimonabant 20 mg once daily in the treatment of atherogenic dyslipidemia [TG ≥ 1.5g/L (i.e. 1.69mmol/L) and ≤ 7.0g/L (i.e. 7.90mmol/L) and/or HDL cholesterol < 50mg/dL (1.29mmol/L) in women, < 40mg/dL (1.04mmol/L) in men] in 740 abdominally obese patients (waist circumference > 102 cm in men and > 88 cm in women). The primary outcome measures were HDL cholesterol and TG plasma levels over a period of one year. Secondary outcome measures were sophisticated lipid measurements, waist and weight measurements, and visceral fat measured by CT scan. Results from the ADAGIO study will be presented at the Congress of the European Atherosclerisis Society in April 2008.

5. Cardiometabolic effects of rimonabant in type 2 diabetes

a. Metformin- or sufonylurea-treated patients : RIO-Diabetes trial

The RIO-Diabetes trial investigated the efficacy and safety of rimonabant in overweight/obese patients with type 2 diabetes [137]. Therefore, 1047 overweight/obese type 2 diabetes patients (BMI 27–40 kg/m^2) with an HbA1c from 6.5 to 10.0% (mean±SD 7.3±0.9% at baseline) already on metformin or sulfonylurea monotherapy were given a mild hypocaloric diet and randomized to placebo or rimonabant (5 or 20 mg) for 1 year. The primary endpoint was weight change from baseline after 1 year of treatment. Secondary endpoints included changes in waist circumference, HbA1c, HDL cholesterol and TG levels (Table 1). Almost two thirds of the diabetic population received metformin as monotherapy, the oral antidiabetic drug considered as first choice in the management of type 2 diabetes [143].

Weight loss (primary endpoint) in the intention-to-treat population was significantly greater after 1 year with rimonabant 20 mg (–5.3±5.2 kg; p<0.001) than with placebo (–1.4±3.6

kg). These weight differences compared favourably with those previously reported with orlistat and sibutramine in overweight/obese patients with type 2 diabetes [144-147]. Rimonabant 20 mg improved HbA1c considered as secondary endpoint (–0.6±0.8% vs +0.1±1.0% for placebo; $p<0.001$) in patients with mean baseline HbA1c of 7.3 %. Treatment with rimonabant 20 mg enabled a greater number of patients to attain the HbA1c American Diabetes Association (ADA) target (HbA1c < 7% : 67.9% vs 47.6% with placebo) and the HbA1c International Diabetes Federation (IDF) target (HbA1c < 6.5% : 42.9% vs 20.8% with placebo). Improvements were almost similar in patients with type 2 diabetes treated with metformin or sulfonylurea at baseline. 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 ($p=0.001$ between groups).

Waist circumference, HDL-cholesterol, TG, fasting glucose levels, HOMA-estimated insulin resistance, systolic blood pressure, and metabolic syndrome prevalence also improved significantly with rimonabant 20 mg vs placebo (Table 2). In addition, a 25% significant reduction in plasma levels of C-reactive protein (CRP), a marker of silent inflammation known as an independent marker of CVD complications, was observed in type 2 diabetic patients treated with rimonabant compared to those receiving placebo, a finding confirming previous observation in dyslipidemic non-diabetic patients [133]. These favourable effects on multiple risk factors are important in order to improve the overall cardiovascular prognosis in this population [31]. These results confirm in overweight/obese patients with type 2 diabetes what was previously observed in the non-diabetic population [114-116]. Again, the HbA1c, HDL-C and TG improvements with rimonabant 20 mg were approximately twice those expected from the observed weight loss alone. The 0.7 % observed reduction in HbA1c levels seen with rimonabant 20 mg vs placebo appears to be greater than the corresponding reduction observed with orlistat or sibutramine in almost similar RCTs [144,145]. Such a reduction is clinically relevant since the United Kingdom Prospective Diabetes Study (UKPDS) showed that each 1% reduction in HbA1c was significantly associated with a reduction in risk of 21% for any clinical endpoint related to diabetes, especially retinopathy and nephropathy [148].

b. **Drug-naïve patients : SERENADE trial**

The favorable effects of rimonabant in type 2 diabetes have been recently confirmed in SERENADE (« Study Evaluating Rimonabant Efficacy in drug-NAive DiabEtic patients »), a 6-month placebo-controlled trial in overweight/obese with recent-onset diabetes treated with diet alone (Table 2) [149]. HbA1c (primary endpoint in this trial) decreased by 0.8 % in the group receiving rimonabant 20 mg compared to 0.3 % in the group receiving placebo (p=0.0002; mean baseline HbA1c 7.9 %). These differences were almost similar to those observed after 6 months in RIO-Diabetes [137] In patients with higher HbA1c levels (≥8.5%) at baseline, impressive reductions of 0.7% and 1.9% were observed in the placebo and rimonabant 20 mg treatment groups, respectively (p<0.001). Similarly to the changes observed in RIO-Diabetes, significant reductions in body weight, waist circumference and TG levels were observed whereas a significant increase in HDL-C was noticed with rimonabant 20 mg. Whereas LDL-C was similar between the treatment groups, LDL particle size was slightly increased with rimonabant, reflecting a reduction in small, dense LDL-C (p=0.0008 vs placebo), as previously shown in RIO-Lipids [133]. Rimonabant also decreased HOMA insulin resistance index and significantly increased plasma adiponectin levels (+1.8 µg/ml, p=0.0001, as it was already reported in the non-diabetic population of RIO-Lipids [133]. After adjustment for body weight, rimonabant 20 mg significantly increased adiponectin and HDL-C levels. Again, almost half of the metabolic improvement occurred beyond weight loss (57% for HbA1c reduction) [149].

c. **Insulin-treated patients : ARPEGGIO trial**

ARPEGGIO is a multicenter, randomized, placebo-controlled, double-blind, parallel-group, fixed-dose study evaluating the effect of one dose of rimonabant (20 mg/day) on glycemic control in type 2 diabetic patients inadequately controlled (HbA1c greater than or equal to 7%) with insulin (insulin dose of at least 30 U/day for at least 4 weeks) (ClinicalTrials.gov Identifier: NCT00288236) [150]. The primary outcome was the effect on HbA1c over 48 weeks. Secondary outcome measures were effects on plasma glucose, total daily insulin dose, body weight, waist circumference, HDL-C, TG, as well as safety and tolerability. This study is completed and the results will be presented at the next American Diabetes Association meeting

in June 2008. As glucose lowering treatment could be adjusted throughout the study, such adjustments should be taken into account to interpret the changes in HbA1c, in addition to other non-glucose related outcomes (body weight, dyslipidemia, blood pressure).

d. **Type 2 diabetic patients : subgroup from ADAGIO**

In the recent ADAGIO trial, which essentially investigated the effects of rimonabant 20 mg on lipid profile and visceral adipose tissue (see above), diabetes was not an exclusion criterion and 17 % of the randomized patients had type 2 diabetes. This study confirmed the positive effect of rimonabant 20 mg on waist reduction and on HDL-C, TG and HbA1c levels, and demonstrated a significant reduction in visceral adipose tissue and liver fat content [142]. This finding is important as far as type 2 diabetes is concerned because fatty liver has been shown to be strongly associated with insulin resistance and profound glucose metabolism dysregulation [105,151].

6. Ongoing and future clinical trials with rimonabant

a. Prevention of type 2 diabetes

After the demonstration that rimonabant was able to attenuate the worsening or even promote improvement of glucose tolerance [138,139], two studies are ongoing to demonstrate that rimonabant 20 mg is able to prevent type 2 diabetes in overweight/obese patients with impaired fasting glucose and/or impaired glucose tolerance (RAPSODI) or in abdominally obese patients with impaired fasting blood glucose (PRADO) As rimonabant targets a key factor in the pathophysiology of the disease, i.e. abdominal obesity and adiposopathy [18,21,152], this effect may be a true preventive effect rather than a delaying or masking effect as previously reported and discussed with various oral antidiabetic drugs [153].

b. Management of type 2 diabetes

Currently available studies have already demonstrated the superiority of rimonabant over placebo in the management of type 2 diabetes in patients on monotherapy with metformin or sulfonylurea (RIO-Diabetes), in drug-naïve patients (SERENADE) and in insulin-treated patients (ARPEGGIO) (see above). Sanofi-aventis has decided to substantially broaden the ongoing

development program in type 2 diabetes with more than 5,700 patients. This new development program in diabetes, essentially as an add-on of rimonabant 20 mg on top of the main existing treatments, includes the following major trials [154] : 1) SOLO is a first line monotherapy study evaluating rimonabant versus placebo in obese diabetic Japanese patients; 2) TOCCATA will evaluate rimonabant versus placebo in combination with metformin; 3) ALLEGRO is evaluating rimonabant versus sulfonylurea in combination with metformin; 4) SYMPHONY is evaluating rimonabant versus placebo in combination with sulfonylurea or an alpha glucosidase inhibitor; 5) RESONATE will evaluate rimonabant versus sitagliptin in combination with metformin; and 6) REASSURE will assess the effect of rimonabant on HbA1c in overweight or obese patients with type 2 diabetes not adequately controlled on two oral antidiabetic agents. It is important that some of these studies compare rimonabant not only with placebo (as in RIO-Diabetes, SERENADE and ARPEGGIO), but also with other oral glucose-lowering agents [155]. New studies are planned to demonstrate the non-inferiority of rimonabant as compared to insulin-secreting agents such as glimepiride (a classical second-generation sulfonylurea) or sitaglipin (a recently launched antagonist of dipeptidylpeptidase-IV, which enhances glucagon-like peptide-1, promotes the incretin effect and enhances insulin secretion). Finally, as metformin is considered as the first choice drug for the management of type 2 diabetes [143], a fixed-dose combination of rimonabant and metformin will also be evaluated in a near future (COMBO trial). Sanofi-aventis expects also to submit a fixed combination of rimonabant plus a statin, in order to obtain a better CVD protection [134]. In all new trials in type 2 diabetes, HbA1c reduction has been chosen as a primary endpoint. These studies will broaden the spectrum of combined therapy with rimonabant in type 2 diabetes and, if conclusive, may support the role of rimonabant as a possible new antidiabetic agent [21-23]. The potential benefit of rimonabant in the management of type 2 diabetes will probably not consist in a greater reduction in HbA1c as compared to other available glucose-lowering agents, but rather in a broader spectrum of effects leading to a reduced cardiometabolic risk. As CRESCENDO (see below) has recruited a large proportion of patients with type 2 diabetes, the results of this trial (expected in 2011) will be of major interest to demonstrate that rimonabant is able to reduce the incidence of major cardiovascular events in this high risk diabetic population.

c. Prevention of progression of atherosclerosis

As CVD represents by far the first cause of mortality in patients with type 2 diabetes [156], it is a major objective to reduce the incidence of myocardial infarction and stroke in this high risk population [24,25,32,33]. Two imaging studies, including patients with type 2 diabetes, are currently assessing the effect of rimonabant 20 mg on surrogate markers of atherosclerosis : the first one uses the coronary intravascular ultrasound (IVUS) technique ("STRADIVARIUS") while the second one focuses on the carotid intima media thickness ("AUDITOR") [154]. The results of the STRADIVARIUS trial will be presented at the Congress of the American College of Cardiology in March 2008. It is obvious that the results of these two trials will be of major importance to support the potential of rimonabant in preventing the progression of atherosclerosis in overweight/obese patients with a high CVD risk.

d. Prevention of cardiovascular complications

Besides these surrogate endpoints, it is of major interest to demonstrate that rimonabant is able to improve the overall CVD prognosis of high risk patients such as those with type 2 diabetes. Weight management [35-38], especially correction of abdominal obesity [15,24,25], is crucial to obtain a global cardiovascular risk reduction, and previous studies have shown that intentional weight loss is able to reduce overall and CVD mortality in patients with type 2 diabetes [157,158]. The ongoing "CRESCENDO" (Comprehensive Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes) RCT will assess whether rimonabant 20 mg can reduce the risk of major CVD events in 17,000 abdominally obese patients with clustering risk factors (at least half with type 2 diabetes) followed for 5 years [159]. The results of this landmark study are expected in 2011. If positive, this study will support the hypothesis that CB1 receptor blockade not only improves the cardiometabolic risk profile, but also reduces CVD morbidity and mortality, and may extend the current indication of rimonabant.

7. Clinical trials with other CB1 receptor antagonists or inverse agonists

Besides rimonabant, two compounds are extensively evaluated in clinical trials, the CB1 receptor inverse agonist MK-0364 (taranabant, Merck) [67] and the CB1 receptor antagonist CP-945,598 (Pfizer) [75]. Two limited randomized controlled trials (reported only as abstracts) in overweight and obese patients showed that MK-0364 at a daily dose of 12 mg may help patients lose weight by increasing resting energy expenditure and reducing food intake [160]. Phase II trials gave encouraging results, but not published yet. In an effort to minimize adverse effects, Merck is studying a 4 mg dose and a 6 mg dose of taranabant in its ongoing large phase III clinical programme. MK-0364 is currently being evaluated in several placebo-controlled RCTs, for instance : 1) a 52-week study to assess the efficacy and tolerability of MK-0364 in maintaining weight loss induced by diet in obese patients; 2) a 2-year study (1-year weight loss followed by 1-year prevention of weight regain) to assess the safety, tolerability, and efficacy of MK0364 in obese patients; and 3) a 1-year investigational drug study to assess weight loss and metabolic improvement in patients with type 2 diabetes.

CP-945,598 [75] has been evaluated in a 6-month, randomized, double-blind, placebo and positive-controlled phase 2b study to assess the effect of various doses of the drug on weight loss in obese subjects. The trial is completed but the results not published yet. The long-term safety and efficacy of CP-945,598 are being evaluated in several randomized, double-blind, placebo-controlled phase III RCTs, for instance : 1) a 2-year study in the treatment of obese subjects; 2) a 14-month study in the prevention of weight regain in obese subjects; and 3) a 1-year study in the treatment of overweight, oral agent-treated subjects with type 2 diabetes mellitus.

Several other CB1 receptor neutral antagonists or inverse agonists are at earlier stages of development. For instance, AVE1625 is being evaluated in a phase II clinical study to assess its 24-week weight-loss effect in abdominally obese subjects with atherogenic dyslipidemia while SLV-319 is being evaluated in phase IIB clinical trials as an anti-obesity and weight-loss agent [16].

8. Safety issues with rimonabant and other CB1 receptor antagonists

The overall safety profile of rimonabant was generally good in the RIO program. Adverse events (AEs) more frequently reported with rimonabant were gastrointestinal, neurological and

psychiatric in nature, but serious adverse events were infrequent [61,64,161]. Overall AE rates were similar across treatment groups, but discontinuation from AEs occurred more frequently with rimonabant 20 mg vs. placebo during the first year (13.6% versus 7.7% in the non-diabetic population) (Table 3). The most commonly reported AEs were depressive disorders [1.9% vs. 0.8%], anxiety [1.0% vs. 0.3%] and nausea [1.4% vs. 0.1%]. Most AEs occurred during the first few weeks-months of rimonabant treatment. During the second year, overall discontinuation rate because of AEs was similar (4.7 %) with rimonabant and placebo in a pooled analysis of RIO-Europe and RIO-North America trials.

In Rio-Diabetes, although overall discontinuation rates were similar, discontinuations due to AEs were more frequent in the rimonabant 20 mg (15.0%) compared with placebo (5.5%) [137]. The most common AEs leading to premature study discontinuation in the rimonabant 20 mg group were depressed mood disorders, nausea and dizziness, thus almost similar AEs as in the non-diabetic overweight/obese population (Table 3). However, no serious AEs linked to psychiatric disorders were recorded in the rimonabant 20 mg group. Hypoglycaemia symptoms were uncommon, although slightly more frequent in the rimonabant-treated group than in the placebo group, essentially in diabetic patients receiving sulfonylureas. Overall, the safety profile of rimonabant 20 mg in SERENADE was comparable to that reported in RIO-Diabetes and in other RIO trials [149].

The overall safety of rimonabant in the RIO program has been extensively reviewed by the principal investigators of the four individual trials [161]. A recently published independent meta-analysis of these 4 RIO trials confirmed that rimonabant caused significantly more adverse events than did placebo (odds ratio or OR = 1.4; p=0.0007) and more serious adverse events (OR=1.4; p=0.03) [162]. In particular, patients with rimonabant 20 mg were 2.5 more likely to discontinue the treatment because of depressive mood disorders than were those given placebo (OR=2.5; p=0.01). Furthermore, anxiety caused more patients to discontinue treatment in rimonabant groups than in placebo groups (OR=3.0; p=0.03).

The overall safety profile of the drug was assessed by the Food and Drug Administration (FDA) leading to a more extensive additional safety set of data [163] The main FDA concern was a higher incidence of suicidal ideation in rimonabant-treated patients as compared to

placebo-treated overweight/obese patients, although the levels remained very low (0.6 versus 0.3 %, respectively). In an updated (but as yet unpublished) analysis of the entire obesity clinical programme with rimonabant, depressive disorders were reported in 3.9% of patients in the rimonabant 20 mg group compared with 1.7% in the placebo group, while mood alterations with depressive symptoms were reported in 4.7% and 2.8% of the rimonabant- and placebo-treated patients, respectively. Most importantly, there was a greater likelihood of developing depressive disorders among patients with a past history of depressive disorders than in patients with no past history. In patients with no such past history, the incidence of depressive disorders was 2.4% in the group receiving rimonabant compared with 1.1% in the group receiving placebo. In contrast, the incidence of depressive disorders in patients with a past history was 19.1% and 8.9% with rimonabant 20 mg and placebo, respectively. Thus it is worth of noting that the risk of depressive disorders was considerably lower in patients without past history of depression but receiving rimonabant 20 mg combined to diet and exercise advice than in patients with a past history of depression and receiving placebo in addition to diet and exercise counselling.

Anxiety and depression most probably result from the pharmacological CB1 antagonist activity of the drug in the brain. Indeed, in spite of the reporting of conflicting results, the pharmacological enhancement of EC activity at the CB1 receptor level appears to exert an antidepressant-like effect in some animal models of depression. On the contrary, a reduced activity of the EC system seems to be associated with an animal model of depression [164]. With regard to clinical studies, several authors have reported an alteration of EC serum levels in depression [164]. Therefore, it is highly probable that the psychological adverse effects reported with rimonabant will also be observed with other CB1 receptor modulators. In a recent study, the acyclic CB1 receptor inverse agonist taranabant (MK-0364) was associated with a dose-related increased incidence of mild to moderate psychiatric adverse events [160]. Whether pure neutral CB1 receptor antagonists, who were shown to be associated with less nausea in animals [56,57], would also have a better safety profile, with the same metabolic efficacy, remains to be investigated in humans.

8. Rimonabant in clinical practice

Rimonabant (Acomplia®, 20 mg), the first of this new class of CB1 receptor antagonists, has been approved by the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMEA) "as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥30 kg/m²), or overweight patients (BMI >27 kg/m²) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia". Furthermore, the Committee recognized that half of the observed improvements in several metabolic parameters (HbA_{1c}, HDL cholesterol and TG) in patients who received 20 mg rimonabant were beyond that expected from weight loss, in agreement with direct peripheral metabolic effects.

However, the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration (FDA) in a review process on June 13, 2007 raised concern about the safety profile of rimonabant (depression, suicidality, neurological adverse events) [163]. Nevertheless, the EMEA recently confirmed the benefit/risk ratio in well selected overweight/obese individuals [165]. However, the post-hoc extensive analysis regarding depression (see above) led to the recent revision by the EMEA to the product label, which states that "*In patients with a history of depressive disorder rimonabant should not be used unless the benefits of treatment are considered to outweigh these risks in an individual patient.*" [165].

Patients most likely to benefit from rimonabant are those with multiple cardiometabolic risk factors known to be improved by the drug, such as abdominal obesity, type 2 diabetes and atherogenic dyslipidemia (low HDL-C and/or high TG) [60,61,63,64]. Rimobanant is not a cosmetic drug and is not indicated for patients with a BMI < 27 kg/m² or for those with a BMI between 27 and 29.9 kg/m² but who have no associated cardiometabolic risk factor(s). Rimonabant is contraindicated for pregnant or breast-feeding women and is not recommended for children below 18 years of age. Moreover, it should not be given to patients with severe renal/hepatic impairment. Because patients with antecedent of depression or receiving antidepressant agents were excluded from the RIO program and because mood disorders were more frequently observed with rimonabant than with placebo in all clinical trials, rimonabant is contraindicated in patients with uncontrolled serious psychiatric illness such as major depression, or patients receiving antidepressant medication. Monitoring for on-treatment anxiety and

depression will be necessary in the future to ensure the safe use of rimonabant or of any other CB1 receptor antagonist.

9. Conclusions

The discovery of the EC system represents a hallmark not only in neuroscience, but also in metabolic research. The exploitation of its numerous physiological and pathophysiological functions is a promising avenue for therapeutic applications. Evidence suggests that CB1 receptor blockade is a novel therapeutic strategy that addresses the underlying mechanisms of both abdominal obesity and cardiometabolic risk, both being strongly associated with type 2 diabetes.

Even if lifestyle intervention is essential, the potential role of rimonabant in overweight/obese patients with type 2 diabetes and high risk cardiovascular disease deserves consideration. Multiple favourable effects have been consistently reported in several placebo-controlled RCTs with greater weight loss, reduced abdominal adiposity, lowering of HbA1c levels, and improvements in HDL-C, TG, C-reactive protein levels, blood pressure and insulin resistance. Most metabolic improvements, especially the reduction in HbA1c and the increase in HDL-C levels, were almost twice that expected from the weight loss alone, consistent with the direct peripheral metabolic effects of the drug reported in numerous animal models. Some of these metabolic effects may be related to rimonabant-induced increase in adiponectin levels. Safety issues mainly concern mild transient digestive side-effects and mood disorders, which contraindicated the use of rimonabant in patients with depression history or on antidepressants.

Current findings already support the use of rimonabant 20 mg, in addition to diet and exercise, as a new approach for the management of type 2 diabetes, being an alternative or an add-on therapy to classical glucose-lowering agents. An extensive clinical research program specifically devoted to type 2 diabetes is going to further support this new strategy. However, rimonabant has to be prescribed to the right patient, ie overweight/obese subjects with cardiometabolic risk factors (particularly type 2 diabetes and atherogenic dyslipidemia) and with no major depressive illness and/or ongoing antidepressive treatment, in order to both maximise efficacy and minimise safety issues. Further ongoing studies should confirm the long-term

efficacy and safety of rimonabant, the first selective CB1 receptor antagonist, especially in patients with type 2 diabetes. Similarly, more information regarding the benefit-risk profile of new CB1 receptor neutral antagonists or inverse agonists is awaited with increasing interest in overweight/obese patients with high cardiometabolic risk.

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Figure 1 : Enzymatic machinery involved in the synthesis and degradation of endocannabinoids

Figure 2 : Central and peripheral effects of endocannabinoid overactivity

Figure 3: Central and peripheral effects of CB1 antagonists or inverse agonists

Figure 4 : Deleterious metabolic effects of EC system overactivity and beneficial effects of a selective cannabinoid type 1 (CB1) receptor antagonist in the improvement of glucose control and atherogenic dyslipidemia in overweight/obese patients with type 2 diabetes.

Figure 5 : Consistent metabolic effects of rimonabant 20 mg compared to placebo in the four

RIO trials. Results are expressed as placebo-subtracted after 1 year (mean ± SD; ITT and LOCF analysis)

Table 1 : Compounds developed as CB1 receptor antagonists or inverse agonists.

Molecule code	References	Generic name	Company	Pharmacological characteristics
SR141716A	(58-64)	Rimonabant	sanofi-aventis	Antagonist + (inverse agonist)
SR147778	(76,78)	Surinabant	sanofi-aventis	Antagonist
AVE 1625	(73)		sanofi-aventis	Antagonist
MK-0364	(67,72)	Taranabant	Merck	Selective inverse agonist
CP-945598	(75)		Pfizer	Antagonist
SLV-319	(77)		Solvay/BMS	Antagonist
AM4113	(56,57,82)			Neutral antagonist
AM251	(71,74)			Inverse agonist
LH-21	(70)			Neutral antagonist

Table 2 : Effects of rimonabant in overweight/obese patients with type 2 diabetes : comparison of the results (placebo-subtracted differences) in the 1-year RIO-Diabetes trial and in the 6-month SERENADE trial.

	RIO-Diabetes (n=1.045)	SERENADE (n=278)
Baseline data		
Caucasians (%)	88.5	84.0
Sex ratio (% men)	49.1	50.5
Age (years)	55.6	56.6
Body weight (kg)	96.3	96.4
BMI (kg/m²)	33.7	34.5
Waist circumference (cm)	109.0	108.8
Time since diabetes diagnosis (years)	5.1	1.3
HbA1c (%)	7.5	7.9
% on metformin monotherapy	65	0
% on sulfonylurea monotherapy	35	0
Delta vs placebo (ITT)		
Follow-up (months)	12	6
Body weight (kg)	-3.9	-3.9
Waist circumference (cm)	-3.3	-4.0
HbA1c (%)	-0.7	-0.51
% patients with HbA1c < 7.0 %	+25.9	+15.7

% patients with HbA1c < 6.5 %	+22.1	+7.8
HDL cholesterol (%)	+8.4	+7.3
Triglycerides (%)	-16.4	-17.3
Glucose (mmol/l)	-0.97	-1.0
Insulin (μU/ml)	-1.1	-2.8
Systolic blood pressure (mm Hg)	-2.3	-1.6
Diastolic blood pressure (mm Hg)	-1.2	-0.6

Table 3 : Adverse events related to gastrointestinal tract, central nervous system and psychology causing discontinuation after year 1 in the three RIO trials in non-diabetic patients (pooled data) and in diabetic patients of RIO-Diabetes.

	Non-diabetic patients		**Diabetic patients**	
Number of patients reporting event (a) (as % of total)	Placebo (N=1254)	Rimonabant 20 mg (N=2164)	Placebo (N=348)	Rimonabant 20 mg (N=339)
Depressed mood disorders and disturbances (b)	1.5	2.9	0.9	3.2
Nausea	<0.1	1.3	0.3	1.5
Anxiety	0.4	1.1	0	0.6
Dizziness	<0.1	0.6	0	0.9
Headache	0.4	0.5	0.3	0.6
Vomiting	<0.1	0.2	0	0.6
Paresthesia	0	0.1	0	0.6

(a) Events reported by at least 0.5% of patients on rimonabant 20 mg in either population

(b) Includes preferred terms depression, major depression and depressed mood