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# Endocannabinoid system and its implications for obesity and cardiometabolic risk

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The endocannabinoid system (ECS) is an endogenous signalling system involved in maintaining energy balance. The ECS works both centrally and peripherally to promote metabolic processes that can lead to weight gain, and recent investigations suggest that obesity may be associated with ECS overactivity. Obesity, in particular, abdominal obesity, is recognized as having a role in potentiating cardiometabolic risk factors and disease progression and is often overlooked as a risk factor requiring early monitoring and management. Adipose tissue is a very metabolically active endocrine organ secreting numerous bioactive molecules, adipocytokines, which can act locally and distally. In the obese state, with the notable exception of adiponectin, these cytokines are released in excess and lead to negative metabolic sequelae, such as the potentiation of atherogenic dyslipidaemia, insulin resistance, and hypertension. Blockade of the cannabinoid type 1 ($CB_1$) receptor with the $CB_1$ receptor blocker, rimonabant, has been shown to reduce overall and abdominal obesity and improve a number of metabolic variables, including glucose tolerance, reduced plasma levels of triglycerides and insulin, and increased levels of high density lipoprotein (HDL) cholesterol and adiponectin. In addition, the pro-inflammatory and pro-atherogenic state is reduced, as evidenced by a reduction in the C-reactive protein and atherogenic ApoB lipoprotein, respectively. Thus, blockade of the $CB_1$ receptor may potentially reduce abdominal obesity and some other associated cardiometabolic risk factors.

## Introduction

The endocannabinoid system (ECS) consists of G protein-coupled, cannabinoid type 1 and type 2 ($CB_1$ and $CB_2$) receptors, their endogenous ligands (endocannabinoids), and the enzymes responsible for their synthesis and degradation.[1] This signalling system, acting both centrally and peripherally, is involved in multiple physiological processes, including regulation of food intake, energy expenditure, and lipid metabolism. These endocannabinoid actions facilitate energy intake and storage.[2] It has been suggested that the activity of the ECS is enhanced in human obesity; thus, overactivity of the ECS may contribute to obesity and its cardiometabolic complications.[3–8]

Obesity, in particular, abdominal obesity, is a major risk factor for cardiovascular disease (CVD) and type 2 diabetes, which are two of the leading causes of morbidity and mortality in the USA.[9–11] Over the past 20 years, the prevalence of obesity in US children and adolescents has increased steadily,[12] with 17% of that population being overweight in 2003–4.[13] More recently, impaired glucose tolerance has emerged as a new major concern in this population.[12] Obesity in childhood and adolescence has been associated with a number of subclinical

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cardiovascular structural and functional changes that include increases in cardiac mass, accelerated atherosclerosis, and endothelial dysfunction.[14–16] Abdominal obesity, in particular, is associated with multiple risk factors which include insulin resistance, dyslipidaemia, hypertension, and a pro-atherogenic and pro-inflammatory state. Accordingly, therapeutic approaches to reduce abdominal obesity may enhance the efficacy of cardiovascular risk-reduction regimens. To that effect, recent advances in the understanding of the role of the ECS in regulating energy balance have led to a number of clinical studies assessing the effects of $CB_1$ receptor blockade in obesity.

Pharmacological blockade of the $CB_1$ receptor activity has the potential to modulate energy balance and thereby favourably impact the risk factors associated with CVD and type 2 diabetes, such as abdominal obesity, dyslipidaemia, elevated fasting plasma glucose, and insulin resistance.

This review will focus on central and peripheral components of the ECS and the biological basis for their involvement in energy balance, lipogenesis, and glucose metabolism, and the associated clinical implications for reducing cardiometabolic risk factors. The effect of rimonabant in obese patients will be examined in view of $CB_1$ receptor effects on multiple cardiometabolic risk factors.

## The ECS

High levels of $CB_1$ receptors are expressed in the central nervous system (CNS)[17] and can also be found in many other tissues, including the liver,[18] pancreas,[5,19] adipocytes,[2,7] gastrointestinal tract,[20] and skeletal muscle.[21,22] $CB_2$ receptors are primarily located in immune cells but may also be expressed in a limited fashion in the brain and other non-immune tissues,[23] including adipocytes.[24] The two best characterized endocannabinoids are anandamide and 2-arachidonoyl glycerol (2-AG). Anandamide is the amide of arachidonic acid and ethanolamine, whereas 2-AG is an arachidonic acid ester.[25–27] A distinguishing feature of the endocannabinoids is that, unlike classic neurotransmitters and hormones, they are not stored, but synthesized on demand from membrane-derived phospholipids.[28] Thus, changes in endocannabinoid synthesis have immediate consequences on endocannabinoid signalling. Following synthesis in the brain, endocannabinoids leave the postsynaptic cell and travel back across the synapse to activate CB receptors on pre-synaptic neurons, a process also referred to as retrograde signalling,[28] in which they inhibit calcium channels and decrease neurotransmitter release,[29] both processes known to occur as a consequence of inhibitory G protein activation. Termination of endocannabinoid action occurs during a two-step process. In the first step, endocannabinoids are taken up into the cell, possibly by a carrier-mediated process, common to both anandamide and 2-AG.[30] In the second step, endocannabinoids are hydrolyzed by specific hydrolases. For anandamide, it is fatty acid amide hydrolase (FAAH),[30,31] and for 2-AG, it is monoacylglycerol lipase.[32]

### Central regulation of appetite

Regulation of appetite and energy intake in the brain is thought to occur on at least two different levels. First, the ECS reinforces the motivation for seeking and consuming highly palatable food, probably through interaction with mesolimbic pathways involved in reward mechanisms.[4] Second, the ECS in the hypothalamus becomes activated after short-term fasting, subsequently stimulating appetite.[4] Evidence for the involvement of $CB_1$ receptors in regulating food intake comes from animal studies in which endocannabinoids directly administered into hypothalamic or mesolimbic brain regions dose-dependently stimulate food intake in pre-fed rats[33,34]; this effect could be blocked using a $CB_1$ receptor blocker.[33] Moreover, in fasted rats, hypothalamic levels of endocannabinoids are elevated and decrease after food intake.[34,35]

### Peripheral metabolism

In addition to the central effects on food intake, $CB_1$ receptors in peripheral tissues suggest an involvement of the ECS in the regulation of energy balance at both the central and peripheral levels (*Figure 1*).[2]

Evidence from several animal studies demonstrates that the effect of the ECS on energy homeostasis cannot be solely explained through its central effects on feeding behaviour and supports the concept of peripheral regulation of energy balance by the ECS.[2,36–39] Administration of a $CB_1$ receptor blocker in several animal models of obesity resulted in a significant and sustained weight loss that could not be solely explained by a reduction in food intake, suggesting that there was also an increase in energy expenditure.[21,36–38,40] This observation prompted a series of studies that further established a role for $CB_1$ receptors in regulating energy expenditure. For example, in mice with diet-induced obesity, long-term administration of a $CB_1$ receptor blocker results in sustained weight loss, with only a transient reduction in food consumption.[38] A role for $CB_1$ receptors in energy balance is also suggested by the observation that $CB_1$ receptor knockout mice have a lean phenotype and are resistant to the development of diet-induced obesity when fed with a palatable high-fat diet.[2,39] This and other evidence stimulated the search for $CB_1$ receptor actions beyond simply reducing food intake outside the CNS. Various studies have demonstrated that $CB_1$ receptors are located in adipose tissue and intestines, as well as the liver, pancreas, and possibly skeletal muscle.[2,18,19,21,40–43]

#### Effect of $CB_1$ receptors on adipocyte function

Evidence from cell culture and animal models supports a role for $CB_1$ receptors in regulating adipocyte metabolism. $CB_1$ receptor mRNA has been found in cultured adipocytes and epididymal fat pads, where receptor stimulation leads to activation of lipoprotein lipase and, thus, mobilization of free fatty acids (FFAs).[2] $CB_1$ receptor mRNA levels are increased in genetic models of obesity,[40] and conversely, adipocyte hypertrophy in

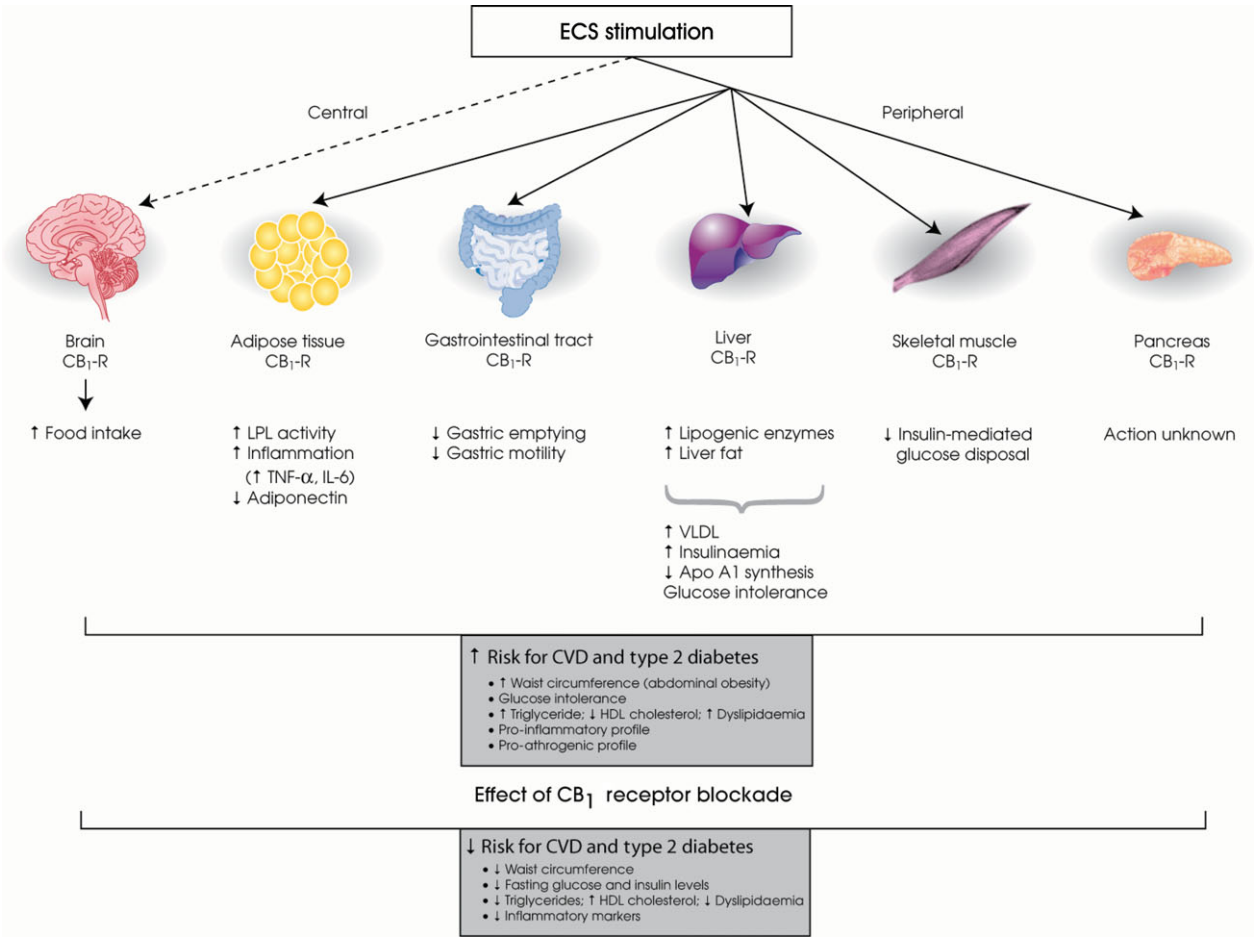


**Figure 1** Effects of overactivity of the endocannabinoid system at both central and peripheral levels and the effect of cannabinoid type 1 receptor blockade on endocannabinoid system actions. In animals, increased activity of the endocannabinoid system has been associated with increased food intake and weight gain; in humans, overactivity of the endocannabinoid system may contribute to obesity and its cardiometabolic complications, such as insulin resistance, dyslipidaemia, and a pro-atherogenic and pro-inflammatory state. Cannabinoid type 1 receptor blockade ameliorates many of these actions and is associated with a risk reduction for cardiovascular disease and type 2 diabetes. $CB_1$-R, cannabinoid type 1 receptor; CVD, cardiovascular disease; ECS, endocannabinoid system; HDL, high-density lipoprotein; IL-6, interleukin 6; LPL, lipoprotein lipase; TNF-α, tumour necrosis factor-α; VLDL, very low density lipoprotein.

mice with diet-induced obesity is reversed following treatment with a $CB_1$ receptor blocker.[44] $CB_1$ receptor blockade also inhibits adipocyte proliferation, at least in cell culture models.[45] Using a global analysis of adipocyte gene transcription, $CB_1$ receptor blockade has been shown to normalize the expression of genes altered during a high-fat diet.[44]

The synthesis and secretion of the hormone adiponectin is an important autocrine function of adipocytes. In humans, adiponectin levels correlate negatively with body mass index (BMI), increased abdominal obesity (visceral and subcutaneous depots), fasting insulin and glucose concentrations, and triglyceride levels.[46–48] Conversely, adiponectin levels in these studies were positively correlated with measures of insulin sensitivity and high density lipoprotein (HDL) cholesterol levels. A decline in adiponectin levels has been implicated in the development of atherosclerosis and glucose intolerance.[46–48] Adiponectin levels are decreased in animal models of genetic and diet-induced obesity, and these changes can be reversed using a $CB_1$ receptor blocker, a change not seen when lean rats or mice are treated in a similar fashion.[40] Thus, $CB_1$ receptor blockade in adipose tissue results in lower FFA concentrations being delivered into the circulation, resulting in reduced fat storage and improved insulin sensitivity.

### Effect of $CB_1$ receptors on intestinal motility

$CB_1$ receptors are also amply expressed in the intestine, where they have a role in regulating gastric emptying and peristalsis.[7,49] There is functional evidence for the presence of $CB_1$ receptors in human ileum longitudinal smooth muscle, where a $CB_1$ receptor agonist potently inhibited the electrically induced twitch response; this effect could be blocked using a $CB_1$ receptor blocker.[41] Activation of intestinal $CB_1$ receptors slows peristalsis and prolongs intestinal transit times; blocking these receptors has a pro-kinetic effect.[20] Similar to observations in the hypothalamus, intestinal anandamide levels increase several-fold following 24 h of starvation.[50] $CB_1$ receptors on intestinal afferents may also play a role in the signalling of satiety. How this effect of $CB_1$

receptor stimulation on intestinal motility affects cardiometabolic risk remains unknown; however, delays in gastric emptying and prolonged intestinal transit times may promote weight gain.

### Effect of $CB_1$ receptors on hepatic lipogenesis

$CB_1$ receptors are present in the liver, where they appear to play a role in lipogenesis.[18] For example, a high-fat diet fed to mice leads to increases in hepatic anandamide, fatty acid synthesis, and $CB_1$ receptor expression.[18] Activation of hepatic $CB_1$ receptors stimulates synthesis of the lipogenic transcription factor SREBP 1c and its associated lipogenic enzymes, acetyl CoA carboxylase and fatty acid synthase.[18] Treatment of mice fed a high-fat diet with a $CB_1$ receptor blocker reduces the increases in fatty acid synthesis normally seen with this diet.[18] As observed in the Rimonabant-in-Obesity (RIO) trials,[51–54] $CB_1$ receptor blockade in the liver may be responsible for the improvements of the dyslipidaemic profile.

### Expression and function of $CB_1$ receptors in the pancreas

The presence of $CB_1$ receptors in the pancreas has been documented[19,55] and several lines of evidence suggest a role for its involvement in glucose homeostasis. Treatment with a $CB_1$ receptor blocker decreased insulin levels in mice with diet-induced obesity[37,39] as well as in obese Zucker rats[40]; in the former group, $CB_1$ receptor blockade also decreased serum glucose levels.[37] However, the mechanism by which $CB_1$ receptor antagonism decreases serum insulin levels and enhances insulin sensitivity remains to be determined.

### Effect of $CB_1$ receptors in skeletal muscle

$CB_1$ receptor mRNA has recently been reported in skeletal muscle of mice, with higher levels in mice with diet-induced obesity compared with lean mice.[22] Administration of a $CB_1$ receptor blocker in *ob*/*ob* mice increased basal oxygen consumption and glucose uptake by skeletal muscle, possibly suggesting that $CB_1$ receptor blockade can increase energy expenditure and may improve insulin sensitivity.[21]

In summary, the ECS functions centrally to regulate appetite, and peripherally to modulate adipocyte metabolism, intestinal motility, hepatic lipogenesis, and glucose homeostasis. Furthermore, $CB_1$ receptor stimulation favours an anabolic state promoting fat storage/weight gain and insulin resistance, which are risk factors for CVD.

## The ECS and cardiometabolic risk

Adipose tissue is an active endocrine organ which produces and secretes a host of bioactive molecules, including FFAs, cytokines, plasminogen activator inhibitor 1, leptin, and adiponectin.[56] With the exception of adiponectin whose levels decrease in obesity, these adipokines are overabundant in obesity,[56,57] and when secreted in excess, can adversely affect health.[56]

Thus, studies have suggested that abdominal obesity presents an important predictor of overall health risk and mortality compared with generalized overweight or obesity.[56] Abdominal obesity is a major risk factor for multiple cardiometabolic risk factors that include insulin resistance, dyslipidaemia, hypertension, and a pro-atherogenic state with elevated ApoB lipoprotein levels and a pro-inflammatory state with elevated C-reactive protein levels.[58] There is a continuum of risk towards the progression of CVD and metabolic disease; thus, early recognition and treatment of obesity is important.[59]

In this regard, obesity, in particular during childhood or adolescence, is often a consistent predictor of cardiovascular and metabolic dysfunction developing at a later stage in life, including left ventricular hypertrophy (LVH),[15,16] increased carotid artery intima-media thickness,[60] coronary atherosclerosis,[14] and endothelial dysfunction.[61] For example, both the Bogalusa Heart Study[16] and the Strong Heart Study[15] demonstrated that obesity during childhood and adolescence was a significant predictor of LVH and possibly also of reduced myocardial performance in adulthood. In the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, a BMI $>30$ kg/m$^2$ in young men (15–34 years) was associated with fatty streaks, raised lesions, and stenoses in coronary arteries, all signs of accelerated atherosclerosis.[14] The Mexico City Diabetes Study, which included non-diabetic, pre-diabetic, and diabetic patients, assessed the relationship between carotid artery intima-media thickness and the onset of clinical diabetes.[60] Relative to non-diabetic individuals, pre-diabetic patients had a higher BMI, larger waist circumference (WC), higher insulin and glucose levels, and a worse lipid profile. More importantly, internal carotid artery intima-media thickness was significantly higher among the pre-diabetic individuals compared with subjects who remained free of diabetes.[60]

The link between obesity and the ECS is still unresolved. In obese women, circulating anandamide and 2-AG levels are increased, whereas adipose $CB_1$ and FAAH (the primarily anandamide-degrading enzyme) mRNA are decreased.[7] Moreover, in a study of $>2500$ subjects, a mutation in the FAAH gene was observed approximately twice as often in overweight and obese individuals when compared with normal weight individuals.[6] It has been postulated that overactivation of the ECS, and thus $CB_1$ receptor activity, in obesity results in adipocyte hypertrophy[44] and markedly reduced plasma adiponectin levels, a common feature of abdominal obesity and insulin resistance.[46] Hypo-adiponectinaemia, in turn, has been implicated in a pro-atherogenic and pro-inflammatory state that includes low HDL cholesterol levels,[46] endothelial dysfunction,[62] and elevated fasting glucose.[63,64] Moreover, an overactive ECS has also been linked to hepatic lipogenesis,[18] where it may contribute to fat accumulation in the liver, leading to non-alcoholic steatohepatitis (NASH), a well-known consequence of insulin resistance, type 2 diabetes, and hyperlipidaemia.[65]

Thus, the current evidence supports a role of an overactive ECS in obesity and the development of NASH, insulin resistance, and atherogenesis. Consequently, $CB_1$

receptor blockade is an attractive target to ameliorate multiple cardiometabolic risk factors.

## Obesity and cardiovascular risk

Physicians are more familiar with established risk factors for coronary heart disease, such as hypertension, dyslipidaemia, and type 2 diabetes, and have at their disposal an array of drugs to treat them. However, current therapeutic strategies for risk factor management are reactive, focusing on clinically evident risk factors in isolation. Although individual treatment goals may be met with this approach, many patients experience a significant residual cardiovascular risk. In several cardiovascular outcomes studies, up to 24% of patients still experienced cardiovascular events.[66–70]

The Heart Outcomes Prevention Evaluation (HOPE) study evaluated the effects of angiotensin-converting enzyme (ACE) inhibition on cardiovascular risk reduction in more than 9000 patients with vascular disease or type 2 diabetes. Although there was a 22% risk reduction in the ACE-inhibitor-treated group after 5 years, 14% of patients in this group reached the primary endpoint of this study, myocardial infarction (MI), stroke, or death from cardiovascular cause.[70] In comparison, in the Heart Protection Study,[68] simvastatin use in more than 10 000 patients was associated with a 24% reduction in coronary mortality, MI, stroke, and revascularization procedures. Although this was impressive, over the 5-year study period, almost 900 non-fatal MIs occurred in this group, constituting a substantial 19.8% residual risk. In the Steno-2 Study,[69] both behavioural and pharmacological approaches were taken to target dyslipidaemia, hyperglycaemia, hypertension, and microalbuminuria in patients with type 2 diabetes and microalbuminuria. After almost 8 years, patients receiving intensive therapy had a 47% reduced risk of CVD compared with those receiving usual care. However, the residual risk of a cardiovascular event was still 24% in the intensively treated group. Interestingly, despite being exposed to a multifactorial intervention programme, patients in the Steno-2 study did not lose any weight, emphasizing the difficulty associated with achieving lasting weight loss.

The PROVE IT-TIMI 22 study, a state-of-the-art secondary prevention trial, assessed the risk of recurrent myocardial events and the relationship between low density lipoprotein (LDL) cholesterol and C-reactive protein levels in statin-treated patients with acute coronary syndromes. Fewer statin-treated patients with LDL cholesterol levels $<$70 mg/dL had recurring myocardial events (5.4%) compared with patients with higher cholesterol levels (7.4%).[67] Patients with LDL cholesterol $<$70 mg/dL and C-reactive protein levels $<$1 mg/L had the lowest event rate (3.8%). A follow-up to the PROVE IT-TIMI 22 study found that the highest C-reactive protein levels are found in patients with features of obesity and/or insulin resistance, such as a high BMI, low HDL cholesterol, high triglycerides, high fasting glucose, and hypertension.[66] This study demonstrates that despite conventional and maximal prevention drug therapy, obesity- and insulin-related risk factors may have a significant role in residual cardiovascular risk. Thus, obesity and insulin resistance should also be targets for intervention, in addition to those listed in the current secondary prevention guidelines.

## Benefits of weight loss and lifestyle management

Even moderate weight loss has been shown to beneficially impact multiple cardiometabolic risk factors, leading to an overall reduction of cardiovascular risk.[71–73] For example, a 5–10% loss of body weight has been associated with a decrease in circulating levels of inflammatory cytokines, improved fasting glucose and insulin levels, improved endothelial function,[72] lower blood pressure,[74,75] and an improved lipid profile.[71] In addition, weight loss has been shown to prevent type 2 diabetes in the Diabetes Prevention Program.[76] Perhaps most importantly, weight loss was associated with a significant reduction in all-cause mortality in markedly overweight men, and the data suggest that the earlier the intervention, the greater the chance of benefit.[77] However, although several large studies have demonstrated that CVD risk could theoretically be reduced by $>$80%[78] or even $>$90%[78] if individuals adhered to a healthy lifestyle that includes regular exercise, a healthy diet, abstaining from smoking, consuming small amounts of alcohol, and reducing day-to-day stress, most people were unable to do so over a long-term period. In fact, in the Nurses Health Study, only 3% of women met those criteria.[78] Because it is inherently difficult for overweight and obese individuals to lose weight and improve their cardiometabolic risk profile, effective pharmacotherapies would be beneficial.

## Therapeutic application of the $CB_1$ receptor blocker rimonabant

The four RIO trials were large multicentre, multinational trials that assessed the efficacy and safety of the $CB_1$ receptor blocker rimonabant in reducing body weight and positively modifying multiple cardiometabolic risk factors in obese patients.[51–54] The four studies included more than 6000 overweight and obese patients, with or without co-morbidities, who received rimonabant (20 mg/day) for 1 year or longer. At the end of the studies, patients demonstrated a significant reduction of overall body weight and, more importantly, a substantial reduction of abdominal obesity, as evidenced by a reduction in WC. This loss of abdominal adipose tissue was accompanied by marked improvements in metabolic parameters, including a reduction in triglycerides, fasting glucose,[53] HbA1c,[54] and insulin levels.[51–54] At the same time, patients receiving rimonabant 20 mg demonstrated a significant increase in HDL cholesterol[51,53,79] and adiponectin[51] levels. In addition, rimonabant therapy reduced pro-atherogenic and pro-inflammatory risk, as evidenced by a shift in the distribution of LDL-cholesterol particles

towards a larger size (a 4.6% reduction of atherogenic small LDL particles) and a decrease in C-reactive protein, respectively.[51]

The metabolic improvements produced by rimonabant 20 mg treatment were greater than would have been expected from weight loss alone. For example, only ~50% of the changes in HDL cholesterol, triglyceride levels, fasting insulin levels, and insulin resistance could be attributed to weight loss.[52] In patients receiving rimonabant for 2 years, weight loss stabilized after 1 year; however, HDL cholesterol continued to increase.[52] These findings suggest a weight-loss-independent effect of $CB_1$ receptor blockade with rimonabant on metabolic risk.

Furthermore, the percentage of patients with a diagnosis of metabolic syndrome (according to the criteria of the Adult Treatment Panel III)[80] decreased from 54% at baseline to 26% after 1 year in the rimonabant 20 mg group. This decrease was significantly greater than in the placebo group and was largely attributed to a reduction in WC and an increase in HDL cholesterol.[51]

Rimonabant was generally well tolerated. Treatment-related adverse events (AEs) most commonly reported with rimonabant 20 mg were similar across all four trials[51–54] and included nausea, dizziness, diarrhoea, insomnia, and anxiety. Discontinuations due to AEs over 1 year of treatment were higher in the rimonabant 20 mg group. The most common AEs leading to study discontinuation were depressed mood disorders in all treatment groups. Discontinuations due to nausea, vomiting, diarrhoea, headache, dizziness, and anxiety were more frequent in the rimonabant (20 mg/day) group than in the other groups. Although the 1-year discontinuation rate was high (33–49%), these numbers are comparable with other obesity trials and were actually slightly lower in the rimonabant group when compared with placebo. In the 2-year RIO North America study, discontinuations due to AEs in the second year were $<5\%$ in all groups and did not vary among treatment groups.[52]

## Conclusion

Abdominal obesity is associated with increased risk of developing type 2 diabetes and CVD. The ECS, an endogenous signalling system implicated in the regulation of energy balance, appetite, hepatic lipogenesis, and glucose homeostasis, has been suggested to be overactive in patients with obesity, promoting a state that favours metabolic processes leading to weight gain, lipogenesis, insulin resistance, and dyslipidaemia. Treatment with the $CB_1$ receptor blocker rimonabant 20 mg for 1 year, reduced body weight and WC and improved multiple cardiometabolic risk factors, as evidenced by significant reductions in triglycerides, fasting insulin, HbA1c, blood pressure, and beneficial increases in HDL cholesterol and adiponectin. Therapeutic strategies targeting the ECS have the potential to delay the onset and progression of type 2 diabetes and CVD.

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