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COMMENTARY

Rimonabant in rats with a metabolic syndrome: good news after the depression

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The synthetic cannabinoid CB_1 receptor antagonist rimonabant (sold in the United Kingdom under the brand name Acomplia) was reported to improve the profile of cardiovascular risk factors in obese patients with the metabolic syndrome, a cluster of metabolic disorders that often precedes the onset of type II diabetes. Rimonabant is shown in the current issue of *British Journal of Pharmacology* to attenuate weight gain in Zucker rats, an experimental model of insulin resistance. Neutrophil and monocyte counts were lowered by rimonabant administration. Both platelet activation (by ADP) and aggregation (in response to thrombin) were inhibited. Circulating pro-inflammatory cytokine levels (monocyte chemotactic protein 1, MCP1 and Regulated upon Activation, Normal T-cell Expressed and Secreted, RANTES) were also reduced. Furthermore, fibrinogen levels returned to normal. These favourable anti-inflammatory and anti-thrombotic actions imply for rimonabant a peripheral, direct action on some cardiovascular risk factors.
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In the industrialized world, the prevalence of obesity has reached epidemic proportions. In the United Kingdom, almost half of the adults will be obese by 2015, and this, the *British Medical Journal* warns, could bankrupt the National Health Service (Lean *et al*., 2006). Obese people are at high risk of multiple health problems: most importantly, rampant obesity is thought to be responsible for the dramatic rise in the incidence of type II diabetes (T2D). Indeed, abdominal obesity is a key component in the metabolic syndrome (also known as insulin resistance syndrome), a cluster of metabolic disorders (including large waistlines, high triglycerides and fasting glucose, low high-density lipoprotein cholesterol and high blood pressure) that often precedes T2D (Després and Lemieux, 2006). The molecular pathogenesis of the metabolic syndrome is complex and poorly understood. At the clinical level, patients with this cluster of disorders have atherogenic inflammation and are in a pro-thrombotic state. Consequently, coronary artery disease and other potentially fatal cardiovascular thrombotic events (for example, stroke and peripheral vascular disease) are also common, justifying a new definition of the metabolic syndrome as a part of the global 'cardiometabolic' risk. In particular, high abdominal ('apple-like') obesity and visceral fat have been linked to the metabolic syndrome (Després and Lemieux, 2006). Reversal of the rising trend in the prevalence of obesity is of the utmost importance. Unfortunately, many people are unable to lose their excess weight by diet and exercise alone. Therefore, medical practice must adapt to the obesity epidemic by developing new pharmacological and surgical (for example, bariatric surgery) interventions and by addressing the problem of visceral obesity and related metabolic disorders (Lean *et al*., 2006). The antagonism of cannabinoid CB_1 receptors is one example of such strategies, although with some complications (see Matias and Di Marzo, 2007).

Rimonabant (SR141716) is a synthetic cannabinoid CB_1 receptor antagonist developed by Sanofi-Aventis (Paris, France), which has been tested so far in four published obesity trials (RIO, Rimonabant In Obesity) involving over 2500 obese patients (Van Gaal *et al*., 2008). It has been available in the United Kingdom since July 2006 under the brand name Acomplia. In the United Kingdom, it is indicated for use in patients whose body mass index exceeds $30\,kg\,m^{-2}$ or who have associated risk factors such as T2D and/or dyslipidaemia. In other countries, such as Sweden, obesity alone is not an indication for Acomplia, and abnormal blood lipid levels are also required for the prescription. As of early 2008, rimonabant is available in almost 40 countries worldwide. The most notable exception is the United States where an advisory Food and Drug Administration (FDA) panel concluded that the manufacturer failed to demonstrate the safety of rimonabant. Of particular concern was the increased incidence of the signs of

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depression (from 1.6 to 3.2% according to data pooled from the four RIO studies; Van Gaal *et al*., 2008) in patients on rimonabant. Yet, many clinicians believe that the beneficial actions of rimobanant on cardiometabolic risk outweigh its side effects. Thus, as previously reviewed (Matias and Di Marzo, 2007), the RIO-Lipids trial enrolled 1036 men and women who had untreated dyslipidaemia and a body mass index between 27 and 40 kg m^{-2}, and examined the effects of rimonabant on several cardiometabolic risk factors, including high C-reactive protein and low adiponectin levels. Compared with the placebo group, subjects treated with rimonabant (20 mg daily for 1 year) had significant weight loss, increased 'good' high-density lipoprotein cholesterol and a reduction in plasma triglycerides, as well as significant reductions and increases in plasma C-reactive protein and adiponectin levels, respectively. A retrospective analysis of these data suggests that the increase in adiponectin was independent of the weight loss. The RIO-Europe trial enrolled and randomized over 1500 patients to receive either placebo or rimonabant. Patients taking rimonabant maintained significant reduction in body weight (15–20 lb compared with 5 lb in the placebo group) and, after 2 years, also showed a 30% increase in high-density lipoprotein cholesterol. Even more impressive, the proportion of patients with metabolic syndrome was reduced by 50% by the end of the trial.

The mechanisms by which rimonabant improves the profile of cardiometabolic risk factors in obese patients are subject to intensive research and appear to be largely mediated by the reduction of the overactivity of peripheral CB_1 receptors (Matias and Di Marzo, 2007). In contrast, the worrisome side effects of rimonabant are centrally mediated. Therefore, a yet-to-be-developed CB_1 antagonist that does not cross the blood–brain barrier might exhibit an even better benefit to risk ratio.

In this issue of the *British Journal of Pharmacology*, Schäfer *et al*. (2008) report that rimonabant administered orally (10 mg kg^{-1}) for up to 6 months attenuates weight gain in obese Zucker rats, an experimental model of insulin resistance/metabolic syndrome and, in older rats, also prevents T2D. More importantly, the authors looked for the first time at several parameters of atherogenic inflammation and pro-thrombotic state. They observed that neutrophil and monocyte counts were significantly increased in obese or T2D Zucker rats compared with lean controls and were lowered by rimonabant treatment. Furthermore, rimonabant inhibited platelet activation by ADP (as determined by P-selectin expression) in the obese Zucker rats and reduced circulating pro-inflammatory cytokine (MCP1, monocyte chemotactic protein 1 and RANTES, Regulated upon Activation, Normal T-cell Expressed and Secreted) levels. Aggregation of platelets in response to thrombin increased from 3.9% (lean controls) to 41.4% (obese rats), and this increase was reduced to 16.9% in the rimonabant-treated animals. Fibrinogen levels returned to normal in obese rats on rimonabant. These changes are very favourable. Monocytes are precursors to foam cells in atherosclerotic lesions, and activated platelets adhering to damaged endothelium that covers the atherosclerotic plaques are instrumental in promoting further monocyte adhesion. Both MCP1 and RANTES are produced in atherosclerotic lesions and act as chemotactic factors to attract leukocytes that, in turn, promote the progression of vascular damage. In addition, platelet activation and aggregation are crucial steps in thrombus formation leading to coronary artery disease and acute myocardial infarction. Fibrinogen is an acute-phase reactant and as such is a marker of low-grade inflammation. The presence of elevated fibrinogen levels in obese rats with metabolic syndrome lends further experimental support to the concept that these closely related disease states (obesity, metabolic syndrome, T2D and atherosclerosis) share an inflammatory component. Rimonabant appears to reduce cardiovascular risk by disrupting this vicious cycle.

Chronically administered rimonabant is believed to reduce body weight in obese rodents mostly via central nervous system-independent effects that might (1) involve increased lipolysis from the adipose tissue and enhanced energy expenditure (Herling *et al*., 2008); and/or (2) underlie an endocannabinoid overactivity in the visceral adipose tissue, liver and skeletal muscle of obese individuals (Matias and Di Marzo, 2007). Therefore, although Schäfer *et al*. (2008) did not investigate if the effects they observed with rimonabant could be dissociated from inhibition of food intake and/or body weight loss (for example, by using 'pair-fed' animals), it is likely that also in this study this compound exerted its beneficial actions via peripheral mechanisms. In view of the key role played by adiponectin in atherogenic inflammation, the increase in the plasma levels of adipokine, along with the corresponding reduction in tumor necrosis factor-alpha (TNF-α) levels previously observed in Zucker rats treated for several weeks with rimonabant (Gary-Bobo *et al*., 2007), might underlie a large part of the anti-inflammatory effects observed by Schäfer *et al*. (2008). However, direct actions on macrophages/monocytes are also possible. Indeed, based on recent findings that the activation of the other endocannabinoid receptor, CB_2, reduces monocyte chemoattractant properties and monocyte–endothelial cell adhesion (Rajesh *et al*., 2007), the authors speculate that this mechanism might be involved in the anti-inflammatory actions of rimonabant 'by alternative signalling through CB_2 receptors in the presence of functional CB_1 blockade'. The possibility that a reduced tone at CB_1 'unchains' functional activation of other endocannabinoid receptors is intriguing. However, data supporting this mechanism are still lacking, and one should bear in mind that also antagonism of CB_2 receptors has anti-inflammatory actions (Lunn *et al*., 2008). Regarding the platelet-inactivating effects observed by Schäfer *et al*. (2008), they might be explained by the previous observation that the endocannabinoid 2-arachidonoylglycerol (2-AG), whose levels are higher in the blood of obese or T2D patients (Matias and Di Marzo, 2007), stimulates platelet activation in a way partly mediated by CB_1 receptors (Maccarrone *et al*., 2001).

Another potential target for some endocannabinoid actions is the TRPV1 receptor (transient receptor potential, vanilloid subfamily member 1), for which there is emerging evidence for a role in obesity and diabetes (Suri and Szallasi, 2008). Selective ablation of TRPV1-positive pancreatic islet-innervating fibres improves glucose tolerance in diabetic

Zucker rats, an effect observed also with a TRPV1 receptor antagonist (see Suri and Szallasi, 2008). Conversely, the activation of TRPV1, in this case in white adipocytes, inhibits adipogenesis and TRPV1 knockout mice are resistant to high-fat-induced obesity (see Suri and Szallasi, 2008). Thus, either direct antagonism of TRPV1 (De Petrocellis *et al*., 2001) in islet-innervating fibers or indirect adipocyte TRPV1 activation following CB_1 blockade (similar to that postulated above for CB_2 receptors) might explain some of the beneficial metabolic effects of rimonabant and, subsequently, part of the anti-inflammatory actions observed by Schäfer *et al*. (2008).

Regardless of the underlying mechanism, the reduction by rimonabant of markers of a pro-inflammatory and pro-thrombotic state in an animal model of the metabolic syndrome is, potentially, a finding of the utmost clinical importance. Clinical trials aimed at assessing the effect of rimonabant on atherosclerotic plaque thickness and the rate of cardiovascular events in patients at high cardiometabolic risk are ongoing and will define further the therapeutic relevance of this finding.

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