British Journal of Pharmacology (2007) 150, 535–537
 0007–1188/07 $30.00
www.brjpharmacol.org

COMMENTARY

Rimonabant: more than an anti-obesity drug?

B Costa

Department of Biotechnology and Bioscience, University of Milano-Bicocca, Milano, Italy

The endocannabinoid system modulates many pathophysiological functions, including the brain pathways involved in the regulation of body weight and adipose tissue function. The selective cannabinoid CB_1 receptor antagonist, rimonabant, has undergone phase III clinical testing as anti-obesity drug. Obesity is considered a mild inflammatory condition and predisposes individuals to an increased risk of developing many diseases. It has been recently suggested that a successful intervention to treat obesity is a therapy combining weight-reducing drugs with anti-inflammatory ones. In this scenario, rimonabant's anti-obesity action is accompanied by favorable changes in markers for insulin resistance, C-reactive protein, adiponectin, tumor necrosis factor α (TNFα). The results reported by Croci and Zarini in this issue highlight the anti-inflammatory and anti-hyperalgesic effect of rimonabant in obese animals, so suggesting that it could provide a more general and aggressive strategy to protect obese patients from many pathological risks.
British Journal of Pharmacology (2007) **150,** 535–537. doi:10.1038/sj.bjp.0707139; published online 22 January 2007

Keywords: cannabinoid; diabetes; inflammation; obesity; pain; rimonabant

Abbreviations: TNFα, tumor necrosis factor α; TRPV1, transient receptor potential vanilloid type 1

Rimonabant is a selective cannabinoid CB_1 receptor antagonist that has undergone extensive testing in the treatment of obesity in human subjects. The story of rimonabant as an anti-obesity compound begins with the understanding that the endocannabinoid system (cannabinoid receptors and their endogenous ligands) plays a significant role in stimulating appetite through both central and peripheral mechanisms (see Di Marzo and Matias, 2005 for review). The rimonabant in obesity (RIO) program consisted of four phase III clinical trials (RIO-Europe, RIO-Lipids, RIO-North America and RIO-Diabetes) that compared rimonabant (5–20 mg per day) with placebo and showed that rimonabant reduced bodyweight and improved cardiovascular and metabolic risk factors in both non-diabetic overweight or obese patients and in overweight and obese subjects with type II diabetes, inadequately controlled by metformin or sulphonylureas (Scheen *et al.*, 2006 for RIO-Diabetes results; Gadde and Allison, 2006 for review).

Obesity predisposes individuals to an increased risk of developing many diseases, including atherosclerosis, diabetes and some immune-mediated disorders. Importantly, obesity is associated with chronic inflammatory responses, such as arthritis and Crohn's disease (Mokdad *et al.*, 2003; Mehrotra *et al.*, 2004), which are characterized by abnormal cytokine production, increased synthesis of C-reactive protein and the activation of pro-inflammatory signalling pathways (Wellen and Hotamisligil, 2005). Many of these inflammatory mediators are produced through a complex network involving both immune and metabolic systems. In fact, adipose tissue is no longer considered to be an inert tissue, but it is emerging as an important factor in the regulation of many pathological processes. Various products of adipose tissue have been described and, among these, certain cytokines mainly produced by the adipocytes have been named adipocytokines, particularly adiponectin and leptin. Other products of adipocytes include tumor necrosis factor-α (TNFα), interleukin-6, interleukin-1, mediators of the clotting process and certain complement factors (Wellen and Hotamisligil, 2005). The adipose tissue of obese individuals also contains a large number of macrophages, recruited by a chemokine released by adipocytes (CCL2), which are an additional source of cytokines (especially TNFα) in the adipose tissue.

Adiponectin, exclusively produced by adipocytes, regulates the expression of many pro- and anti-inflammatory cytokines. Its main anti-inflammatory effect might be related to its capability to suppress the synthesis of TNFα and interferon-γ, and to induce the production of anti-inflammatory mediators such as interleukin-10. Consequently, many diseases have been associated with a reduced level of adiponectin, including inflammatory bowel disease and rheumatoid arthritis. The role of leptin in regulating inflammatory responses is incompletely understood even though there is an increased expression of leptin in conditions associated with the release of pro-inflammatory

Correspondence: Professor B Costa, Department of Biotechnology and Bioscience, University of Milano-Bicocca, Piazza della Scienza 2, 20126 Milano, Italy.
E-mail: barbara.costa@unimib.it
Received 17 November 2006; revised 22 November 2006; accepted 1 December 2006; published online 22 January 2007

cytokines, particularly in animal models of experimental autoimmune encephalomyelitis, antigen-induced arthritis or experimentally induced colitis. Its role as pro-inflammatory molecule in addition to regulating neuroendocrine function, energy homeostasis, haematopoiesis and angiogenesis, has become increasingly evident and has been recently reviewed (La Cava and Matarese, 2004). Together, these findings suggest that there are important pathways that link metabolism with the immune system and vice versa.

In this issue of *British Journal of Pharmacology*, Croci and Zarini (2007) add an important new insight, such as the anti-inflammatory and anti-allodynic effect of rimonabant in adjuvant-induced arthritis in obese rats. The demonstration that the obese rats showed a greater arthritic score than the lean rats after the inflammatory stimulus supports the view that obesity has to be considered a mild inflammatory condition. They also showed that, after 7 days of repeated oral treatment, rimonabant (3 and 10 mg kg^{-1}) reduced the body weight concomitantly decreasing the severity of arthritis (lower global arthritic score and joint width, with no effect on paw edema) in obese but not in lean rats. This result strongly suggests that rimonabant may have a selective effect in reducing inflammation associated with the pathological condition of obesity. The increased leptin and TNFα plasma levels as well as the decreased adiponectin level, observed in obese subjects may contribute to their increased susceptibility to inflammation (Hauner, 2005). It has been established that rimonabant stimulated adiponectin mRNA expression in obese rats through a direct effect on adipocytes (Bensaid *et al*., 2003) and that it increased the plasma adiponectin in obese patients (Despres *et al*., 2005). This might be the result of the reversal of the inhibitory effect on adiponectin expression by permanently elevated endocannabinoid levels, recently observed in hypertrophic adipocytes (Matias *et al*., 2006). Indeed, a higher tone of the endocannabinoid system has been observed in obese rodents, both in the adipose tissue and in other organs (Di Marzo and Matias, 2005; Osei-Hyiaman *et al*., 2005; Matias *et al*., 2006), and this might explain also the higher efficacy of rimonabant as an anti-inflammatory drug in obese versus lean animals.

Another important finding emerging from the study of Croci and Zarini (2007) is the antinociceptive effect of chronic treatment with rimonabant. Furthermore, such an effect occurred at doses similar to those shown to inhibit a number of central and/or peripheral cannabinoid CB_1 receptor-mediated responses. Although the drug potently reduced thermal hyperalgesia and mechanical allodynia in both lean and obese arthritic animals, these effects were more prominent in obese than lean rats. We have previously demonstrated the ability of rimonabant to counteract neuropathic pain with a mechanism that was not a direct action on the pain signalling system but a consequence of the capability of the compound to reduce neurogenic inflammation (Costa *et al*., 2005). In neurogenic inflammatory pain, including that of arthritis and neuropathy, many cytokines, especially TNFα, play key roles in the generation and maintenance of hyperalgesia and TNFα-blocking drugs, now used in arthritis therapy, reduce hyperalgesia in peripheral neuropathy. On this basis, I agree with Zarini and Croci that the anti-TNFα effect of rimonabant might contribute to its anti-inflammatory properties and consequently to the relief of pain. In the light of the well-established analgesic properties of CB_1 receptor agonists, it is difficult to explain the anti-hyperalgesic effect of rimonabant, a CB_1 receptor antagonist. However, it is tempting to speculate that in the presence of CB_1 receptor blockade, endogenous cannabinoids might induce analgesia through the activation of CB_2 receptors and/or the desensitization of the transient receptor potential vanilloid type I (TRPV1). This possibility is supported by the recent finding showing an upregulation of the two major endocannabinoids (anandamide and 2-arachidonoylglycerol) in spinal and supraspinal areas of neuropathic animals (Petrosino *et al*., 2006). It will be worthwhile to investigate the possible antinociceptive action of rimonabant in diabetic neuropathy. This suggestion is supported by the recently demonstrated efficacy of rimonabant in type II diabetes patients, where the drug produced a significant reduction in HbA_{1c}, so leading to an improvement of the glycaemic equilibrium that seems crucial in preventing and treating the late complications of diabetes, including the peripheral neuropathy. Notably, such an effect was partially independent of weight loss, with peripheral CB_1 blockade as postulated mechanism (Scheen *et al*., 2006). Indeed, if the potent anti-inflammatory and anti-hyperalgesic effect of rimonabant, shown in animal models, were to be confirmed in humans, such a compound would represent an exciting new opportunity for treatment regimens.

Understanding the mechanisms that lead from obesity to inflammation will have important implications for the design of new therapies to reduce the morbidity and mortality of obesity. It has been recently proposed that a beneficial effect may be obtained by treating obesity with therapies that combine drugs acting on overweight and others acting on inflammation. In this scenario, rimonabant's anti-obesity action is accompanied by favorable changes in markers for insulin resistance, C-reactive protein, adiponectin, TNFα, and presumably on neurogenic inflammation and pain. Thus, it is intriguing to consider rimonabant as an example of a unique class of compounds, as it could provide a more general strategy, aimed at several targets, and a more aggressive strategy, to protect obese patients from many pathological risks and leading to an improved quality of life.

References

Bensaid M, Gary-Bobo M, Esclangon A, Maffrand JP, Le Fur G, Oury-Donat F *et al.* (2003). The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. *Mol Pharmacol* **63**: 908–914.

Costa B, Trovato AE, Colleoni M, Giagnoni G, Zarini E, Croci T (2005). Effect of the cannabinoid CB1 receptor antagonist, SR141716, on nociceptive response and nerve demyelination in rodents with chronic constriction injury of the sciatic nerve. *Pain* **116**: 52–61.

Croci T, Zarini E (2007). Effect of the cannabinoid CB_1 receptor antagonist rimonabant on nociceptive responses and adjuvant-induced arthritis in obese and lean rats. *Br J Pharmacol* **150**: 559–566 (this issue).

Despres JP, Golay A, Sjöström L, for the Rimonabant in Obesity-Lipids Study Group (2005). Effects of Rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* **353**: 2121–2134.

Di Marzo V, Matias I (2005). Endocannabinoid control of food intake and energy balance. *Nat Neurosci* **8**: 585–589.

Gadde KM, Allison DB (2006). Cannabinoid-1 receptor antagonist, Rimonabant, for management of obesity and related risks. *Circulation* **114**: 974–984.

Hauner H (2005). Secretory factors from human adipose tissue and their functional role. *Proc Nutr Soc* **64**: 163–169.

La Cava A, Matarese G (2004). The weight of leptin in immunity. *Nat Rev Immunol* **4**: 371–379.

Matias I, Gonthier MP, Orlando P, Martiadis V, De Petrocellis L, Cervino C *et al.* (2006). Regulation, function, and dysregulation of endocannabinoids in models of adipose and beta-pancreatic cells and in obesity and hyperglicemia. *J Clin Endocrinol Metab* **91**: 3171–3180.

Mehrotra C, Naimi TS, Serdula M, Bolen J, Pearson K (2004). Arthritis, body mass index, and professional advice to lose weight: implications for clinical medicine and public health. *Am J Prev Med* **27**: 16–21.

Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS *et al.* (2003). Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* **289**: 76–79.

Osei-Hyiaman D, De Petrillo M, Pacher P, Liu J, Radaeva S, Batkai S *et al.* (2005). Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. *J Clin Invest* **115**: 1298–1305.

Petrosino S, Palazzo E, de Novellis V, Bisogno T, Rossi F, Maione S *et al.* (2006). Changes in spinal and supraspinal endocannabinoid levels in neuropathic rats. *Neuropharmacology*, doi:10.1016/j.neuropharm.2006.08.011.

Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF (2006). Efficacy and tolerability of Rimonabant in overweight or obese patients with type II diabetes: a randomized controlled study. *Lancet* **368**: 1660–1672.

Wellen KE, Hotamisligil GS (2005). Inflammation, stress, and diabetes. *J Clin Invest* **115**: 1111–1119.