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EDITORIAL

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As the focus of this issue of the CMReJournal, the endocannabinoid system (ECS) has provided unique pharmacological tools that, in combination with moderate dietary restriction, can ameliorate several cardiometabolic risk factors simultaneously in obese and overweight individuals, and do this partly independently of the associated weight loss. These targets include visceral (intra-abdominal) obesity, high plasma triglyceride and low HDL cholesterol levels and several measures of insulin resistance, as well as glycated hemoglobin in type 2 diabetic patients [1-3]. The twelve short articles in this special issue summarize the contents of the corresponding lectures given during the 6th International Chair on Cardiometabolic Risk (ICCR) bi-annual meeting held on June 20-22, 2008, under the theme "The endocannabinoid system (ECS): the evidence relating to its sage targeting in the treatment of cardiometabolic risk". At that time, the future of CB1 receptor antagonists/inverse agonists as unique therapeutics against obesity and related metabolic disorders still seemed very promising, despite existing information about their psychiatric side-effects. At this meeting, renowned experts in the fields of the ECS and cardiometabolic risk research summarized current knowledge of the physiological role of the ECS in the brain and peripheral tissues, and of its malfunctioning in obesity and the accompanying hormonal and metabolic abnormalities. The aim of the meeting was to further our understanding of the mechanisms underlying the efficacy and adverse event profiles of several CB1 receptor antagonists/inverse agonists that were under clinical development at that time, and to outline some principles for optimizing their risk/benefit ratio.

The short articles are organized as mini-reviews, each with key points and/or suggestions for future studies, and reflect the various subjects discussed at the meeting, i.e., 1- the role of the ECS and cannabinoid CB1 receptors in the central nervous system (CNS) and its disorders, including stress and maladaptation to new environmental conditions (articles by B. Lutz and by C. Hillard), and in the control of food intake (T. Kirkham); 2- the involvement of the ECS in peripheral functions not necessarily related to the regulation of energy balance, such as the immune response and bone formation (A. Zimmer), and gastrointestinal function (K. Sharkey); 3- the crucial role of endocannabi-

noids and CB1 receptors in the control of adipocyte function (U. Pagotto), which can be explored also by examining the effects of CB1 antagonists in a dog model of the "metabolic syndrome" (R. Bergman); and 4- the role of CB1 and/or CB2 receptors in liver diseases (S. Lotersztajn) and cardiovascular dysfunctions (P. Pacher), including atherosclerosis (F. Mach). Finally, G. Le Fur, who at the time of the conference was CEO of Sanofi-Aventis, describes the history of the development of the first CB1 receptor antagonist/inverse agonist, rimonabant, as an anti-obesity drug, whereas ICCR Chairman J.-P. Després and ICCR International Academic Board member L. Van Gaal, summarize, based on the available data from clinical trials with rimonabant, who should be the ideal patient for this drug [see also ref. 3]

On October 23, the European Medicines Agency (EMEA) announced the suspension of the marketing authorization of rimonabant (Acomplia) in the European Union, based on the conclusion of the EMEA's Committee for Medicinal Products for Human Use (CHMP) that the benefits of this first-in-its-class compound, indicated as an adjunct to diet and exercise for the treatment of obesity in patients with body mass index (BMI)>30 kg/m^2 and in patients with BMI>27 kg/m^2 and dyslipidemia or type 2 diabetes, "no longer outweigh its risks". A few weeks earlier, Merck had announced that they were also discontinuing the clinical development of their CB1 receptor antagonist/inverse agonist, taranabant, based on safety issues. On November 5, Sanofi-Aventis, the developer of rimonabant, announced the interruption of the clinical trial program with rimonabant, apparently based on the decision of several national health authorities to withdraw patients from the ongoing clinical trials with this compound. On the same day, Pfizer also announced a similar decision regarding yet another compound with a similar mechanism of action, otenabant (CP-945,598), stating that "although Pfizer believes that the CP-945,598 compound has the potential to be a safe and effective treatment for weight management…. the Company has decided to discontinue the development program based on changing regulatory perspectives on the risk/benefit profile of the CB1 class and likely new regulatory requirements for approval." This snowballing of events [4] will likely compromise the future prospect of using CB1 receptor antagonists/inverse agonists not only for treating obesity (the indication they were all originally designed for), but also for the treatment of other cardiometabolic risk factors that, as discussed in this issue, these compounds may target directly and independently of their effects on body weight [3].

Indeed, since the publication of the first phase III studies with rimonabant, additional evidence has emerged pointing to altered CB1 receptor signalling as a key mechanism that contributes to the development of visceral obesity and the associated adipose tissue lipotoxicity, insulin resistance, ectopic fat accumulation (including liver fat) and atherogenic inflammation [5-7]. In obese rodents and humans, the amount of lipogenic endocannabinoids was found to be elevated in visceral adipose depots and reduced in subcutaneous adipose tissue [1, 8, 9], thus possibly contributing to the selective deposition of visceral fat at the expense of subcutaneous fat, which acts as a protective metabolic buffer to cope with excess dietary energy [6]. Activation of CB1 receptors in mature adipocytes decreases adiponectin expression [8], thus potentially contributing to the typical hypoadiponectinemic state of visceral obesity, whereas hepatocyte CB1 receptors are sufficient per se to cause fatty liver, dyslipidemias, as well as insulin and leptin resistance in mice subjected to a high fat diet [10]. High plasma levels of the endocannabinoid 2-arachidonoylglycerol (2-AG) in obese patients are strongly

associated with high visceral obesity independently from BMI, and also with high triglycerides, low HDL cholesterol and insulin resistance [11, 12]. A comprehensive lifestyle modification program leading to substantial waist circumference and visceral fat reduction was recently shown to be accompanied by a strong reduction in 2-AG levels [13]. The causative role of the elevated endocannabinoid tone in visceral adipose tissue in the development of abdominal obesity and, hence, type 2 diabetes and atherosclerosis, is suggested by the finding in animal models that CB1 receptor antagonists/inverse agonists significantly ameliorate the altered metabolic and lipoprotein profiles, and the hepatic, pancreatic and renal damage that accompany obesity [14-16]. Conversely, overactivation of CB1 receptors, induced indirectly by inhibiting the degradation of endocannabinoids, was found to cause hypertriglyceridemia in lean mice [17]. Importantly, blockade of CB1 receptors reduces visceral fat more than total fat or hepatic fat in rats fed a candy diet [18], and inhibits the formation of atherosclerotic plaques in a mouse model of atherosclerosis, in a way independent from its effects on food intake and total cholesterol [19]. These findings in animals were paralleled by data obtained in the ADAGIO-Lipids and STRADIVARIUS clinical trials, which indicated that although rimonabant increases the incidence of psychiatric side-effects, including depression, these are usually mild to moderate in severity, and suggested that patients with high-risk abdominal obesity and no history of depression may represent the ideal therapeutic target for CB1 antagonists in terms of an optimal benefit to risk ratio [20, 21]. It may be pointed out that obesity as well as body weight reduction per se have been linked to an increased incidence of depression [22, 23], and therefore the recent statement of EMEA's CHMP recommending the suspension of the marketing of Acomplia may have overemphasized the risk and, consequently, minimized the benefit of CB1 receptor blockade achieved through the use of rimonabant and other CB1 receptor antagonists with a similar pharmacological profile.

We believe that the twelve articles of this special issue, apart from providing a snapshot of the general role of the ECS in various disorders, including the metabolic syndrome, might also help suggest future strategies for the optimal use of the next generation of these compounds, including non brain-penetrant CB1 antagonists [2], for the safe and efficacious pharmacological treatment of residual cardiometabolic risk.

References

1. Di Marzo V. The endocannabinoid system in obesity and type 2 diabetes. Diabetologia 2008; 51: 1356-67.
2. Pacher P, Mukhopadhyay P, Mohanraj R, et al. Modulation of the endocannabinoid system in cardiovascular disease: therapeutic potential and limitations. Hypertension 2008; 52: 601-7.
3. Van Gaal L, Pi-Sunyer X, Després JP, et al. Efficacy and safety of rimonabant for improvement of multiple cardiometabolic risk factors in overweight/obese patients: pooled 1-year data from the Rimonabant in Obesity (RIO) program. Diabetes Care 2008; 31 Suppl 2: S229-40.
4. Jones D. End of the line for cannabinoid receptor 1 as an anti-obesity target? Nat Rev Drug Discov 2008; 7: 961-2.
5. Ritchie SA and Connell JM. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. Nutr Metab Cardiovasc Dis 2007; 17: 319-26.
6. Després JP, Lemieux I, Bergeron J, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol 2008; 28: 1039-49.
7. Guilherme A, Virbasius JV, Puri V, et al. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol 2008; 9: 367-77.

8. Matias I, Gonthier MP, Orlando P, et al. Regulation, function, and dysregulation of endocannabinoids in models of adipose and beta-pancreatic cells and in obesity and hyperglycemia. J Clin Endocrinol Metab 2006; 91: 3171-80.
9. Pagano C, Pilon C, Calcagno A, et al. The endogenous cannabinoid system stimulates glucose uptake in human fat cells via phosphatidylinositol 3-kinase and calcium-dependent mechanisms. J Clin Endocrinol Metab 2007; 92: 4810-9.
10. Osei-Hyiaman D, Liu J, Zhou L, et al. Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. J Clin Invest 2008; 118: 3160-9.
11. Bluher M, Engeli S, Kloting N, et al. Dysregulation of the peripheral and adipose tissue endocannabinoid system in human abdominal obesity. Diabetes 2006; 55: 3053-60.
12. Côté M, Matias I, Lemieux I, et al. Circulating endocannabinoid levels, abdominal adiposity and related cardiometabolic risk factors in obese men. Int J Obes (Lond) 2007; 31: 692-9.
13. Di Marzo V, Côté M, Matias I, et al. Changes in plasma endocannabinoid levels in viscerally obese men following a 1 year lifestyle modification programme and waist circumference reduction: associations with changes in metabolic risk factors. Diabetologia 2008; Epublication ahead of print.
14. Janiak P, Poirier B, Bidouard JP, et al. Blockade of cannabinoid CB1 receptors improves renal function, metabolic profile, and increased survival of obese Zucker rats. Kidney Int 2007; 72: 1345-57.
15. Osei-Hyiaman D, DePetrillo M, Pacher P, et al. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. J Clin Invest 2005; 115: 1298-305.
16. Poirier B, Bidouard JP, Cadrouvele C, et al. The anti-obesity effect of rimonabant is associated with an improved serum lipid profile. Diabetes Obes Metab 2005; 7: 65-72.
17. Ruby MA, Nomura DK, Hudak CS, et al. Overactive endocannabinoid signaling impairs apolipoprotein E-mediated clearance of triglyceride-rich lipoproteins. Proc Natl Acad Sci U S A 2008; 105: 14561-6.
18. Herling AW, Kilp S, Juretschke HP, et al. Reversal of visceral adiposity in candy-diet fed female Wistar rats by the CB1 receptor antagonist rimonabant. Int J Obes (Lond) 2008; 32: 1363-72.
19. Dol-Gleizes F, Paumelle R, Visentin V, et al. Rimonabant, a Selective Cannabinoid CB1 Receptor Antagonist, Inhibits Atherosclerosis in LDL Receptor-Deficient Mice. Arterioscler Thromb Vasc Biol 2008; Epublication ahead of print.
20. Després JP, Ross R, Boka G, et al. Rimonabant reduces both intra-abdominal adiposity and liver fat and improves cardiometabolic risk factors: the ADAGIO-Lipids trial. Presented at the late breaking session of the 77th European Atherosclerosis Society meeting, Istanbul, Turkey, 2008.
21. Nissen SE, Nicholls SJ, Wolski K, et al. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. JAMA 2008; 299: 1547-60.
22. Chaput JP and Tremblay A. Depression and weight loss: opposite outcome for surgery and rimonabant? Obes Rev 2008; 9: 504-7.
23. Onyike CU, Crum RM, Lee HB, et al. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2003; 158: 1139-47.