

Endocannabinoids, Blood Pressure and the Human Heart

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The effects of exogenous and endogenous cannabinoids on the cardiovascular system have been the focus of extensive research. The direct and indirect effects of cannabinoids on heart and blood vessels depend upon experimental conditions, animal species, and, in humans, clinical background. Cannabinoids decrease blood pressure in hypertensive rodents primarily because of decrease cardiac contractility, leading researchers to postulate a role in the treatment of hypertension and cardiac hypertrophy. Rimonabant, the CB₁ receptor blocker in clinical use in many countries, induced a marked and sustained increase in cardiac contractility and blood pressure in hypertensive rats but, on the contrary, contributed to decrease blood pressure in weight-loss clinical trials especially in obese patients with hypertension. In the midst of the obesity pandemic and from the cardiometabolic point of view, the overactivation of the endocannabinoid system present in intra-abdominal obesity appears to be very harmful. Moreover, novel human findings suggest a relationship between CB₁-mediated overactive endocannabinoid system and nephrovascular damage. Overall, it appears that CB₁ blockade in obese patients behaves as a 'multiplier' of the many beneficial effects of body weight loss induced by a hypocaloric diet and increased physical activity (the 'lifestyle changes' that are so difficult to start and maintain). Thus, the concept – based mostly on experimental results using *in vitro* or animal models – that CB₁-mediated endocannabinoid effects are beneficial for the cardiovascular system should be revised at least in obese patients. The results of long-term clinical trials such as the STRAD-IVARIUS and the CRESCENDO trials will tell whether the improvement in the cardiometabolic risk profile induced by Rimonabant translates into vascular changes, reducing the risk of myocardial infarction, stroke and cardiovascular death in patients with abdominal obesity. Time (and much more work) will tell us much more about cannabinoids and the human heart.

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The effects of exogenous and endogenous cannabinoids on the cardiovascular system have been the focus of extensive research, particularly in the past 5 years. Disappointingly, there is currently only one certainty about cannabinoids and the cardiovascular system: the direct and indirect effects of cannabinoids on heart and blood vessels depend upon experimental conditions, animal species, and, in humans, clinical background. Many discrepancies have been found *in vitro* versus *in vivo* studies and in anaesthetised versus conscious animals: these results have been recently summarised in comprehensive reviews focusing on these aspects (1, 2). Therefore, the focus of this review, enriched with some novel (although preliminary) data from clinical studies, will be endocannabinoids and

the human cardiovascular system, and *in vitro* or animal data will be taken into consideration only where necessary.

Smoking is certainly deleterious to the cardiovascular system. Nevertheless, chronic smoking of cannabis has been associated with lower blood pressure and with symptomatic hypotension that was reversed by elevated dosages of rimonabant (3), the receptor blocker now in clinical use in Europe and a number of other countries. In addition to the negative effect of smoking itself, the conflicting effects of marijuana smoke on atherosclerotic heart disease might depend on the simultaneous activation of cannabinoid receptors CB₁ and CB₂ by Δ^9 -tetrahydrocannabinol (Δ^9 -THC), the major active component of marijuana. Indeed, low doses of Δ^9 -THC

inhibited the progression of established atherosclerotic lesions in a murine model of atherosclerosis (4). Moreover, the function of atherosclerotic plaque-resident and incoming immune cells can be favourably modulated by the activation of CB₂ receptors. In humans, however, the simultaneous Δ⁹-THC activation of CB₁ receptors in the brain can induce, at least in some conditions, a cardiovascular stress response with increased cardiac oxygen consumption and reduced coronary blood flow (5).

We are currently in the midst of an obesity pandemic. Increased visceral adiposity even in overweight (BMI ≥ 25 and < 30 kg/m²) subjects is associated with increased metabolic risk (diabetes and atherogenic dyslipidaemia) and cardiovascular risk (myocardial infarction, ictus and death). This increased cardiometabolic risk in viscerally obese subjects might, at least in part, depend on overactivation of the endogenous cannabinoid system (ECS), as described below. Therefore, special emphasis will be placed here on the available data on endocannabinoids and the cardiovascular system in obese patients.

Endocannabinoids, heart, blood vessels and blood pressure: evidence in humans

Administration of cannabinoids in volunteers caused CB₁-mediated pronounced tachycardia (compared with bradycardia in animals) that was apparently caused by increased circulating noradrenaline (6, 7). Thus the inhibition of the sympathetic nervous system (SNS) observed in animal models appear to be absent in non-anaesthetised humans, and the contrasting documented stimulation of SNS is difficult to explain. We speculate that perhaps it is owing to lower cannabinoid doses used in conscious volunteers?

It is unclear to what extent other receptors, including the vanilloid type 1 receptor, are involved in the resulting overall cannabinoid cardiovascular effects in animals and humans (1, 2). There is evidence that a non-CB₁/CB₂ and non-vanilloid receptor induces inotropic and coronary vasodilatory response that can be blocked by rimonabant (8). Despite expectations, the novel endocannabinoid receptor GPR55, activated by atypical cannabinoids, does not mediate the vasodilator effect (9). Receptors aside, it is interesting that an overproduction of endocannabinoids has been reported in conditions associated with severe hypotension, such as cardiogenic shock or decompensated cirrhosis, where monocytes isolated from the blood of cirrhotic patients were found to contain elevated levels of *N*-arachidonylethanolamine (anandamide), and caused CB₁-receptor-mediated hypotension when injected into rats (10).

The CB₁ receptor appears to mediate a direct negative inotropic effect of cannabinoids on human myocardium: anandamide *in vitro* induced a negative inotropic effect in isolated human atrial heart muscle (11). There is also evidence for the existence of a CB₁-receptor-mediated tonic inhibition of the beta-adrenergic responsiveness of isolated cardiac ventricular muscle in a rat model of biliary cirrhosis (12), where increased local endocannabinoid synthesis could play an important role in the blunted contractile responsiveness of cirrhotic cardiomyopathy. By contrast, anandamide does not induce vasorelaxation in porcine coronary vessels (13) or in human myometrial arteries (14).

In addition to the complexities and discrepancies described above, as well as the wide gaps in our knowledge of cannabinoid effects on the human cardiovascular system, at least three other aspects need to be considered: (i) there are many different endocannabinoids and many more cannabinoid-like substances; (ii) at least three multiple splice CB₁ receptor variants exist in humans (15); and (iii) CB₁ receptors can heterodimerise and this can change the function and overall final effects of cannabinoids (16). Thus, understanding the ECS is not an easy task especially when human beings are considered. Nevertheless, the results of the Rimonabant in Obesity (RIO) trials described below reported a significant decrease in blood pressure especially in hypertensive obese patients, indicating that the blockade of an overactive ECS in human obesity has beneficial cardiovascular effects despite experimental evidence from animal models.

Endocannabinoids and the cardiovascular system in human obesity

Human obesity is strongly associated with increased blood pressure, increased left ventricular mass, and increased cardiovascular events. Moreover, body weight changes are accompanied by blood pressure changes in the same direction (17).

Because the effects of cannabinoids on the cardiovascular system are dependent on the underlying conditions, in obesity, especially when visceral obesity is present, the cardiovascular effects of cannabinoids can be different from what observed in most experimental conditions tested to date. First, the available evidence indicates that an overactivation of the ECS is present in human obesity (18). Surprisingly, and in contrast with the current view of endocannabinoids as 'on demand', locally active, and short-lived substances, increased 2-arachidonoylglycerol (2AG) levels were found in plasma of obese women (18). Such increased circulating cannabinoids were in strong correlation with visceral, intra-abdominal adiposity (19, 20) and related to cardiometabolic risk factors in obese men (20). Indeed, increased production of 2AG has been found particularly in visceral adipose tissue of obese patients (21). This contradiction to the classic view of the ECS, makes understanding the pathophysiological implications appears difficult. The increased synthesis of endocannabinoids is so relevant it can be measured as systemic 'spillover' in the venous blood drawn from an upper limb of obese subjects. We have now more questions than answers. What is the meaning of increased circulating cannabinoids? Is it really just the result of spillover from tissues? What main cell type produces them? Are they carried over by lipoproteins and/or albumin and thus reflect their levels? And, primarily, how much do they affect metabolism, heart, and cardiovascular system?

The prevalent view, based mostly on mouse and rat models, is still that the endocannabinoid system plays an important role in the cardiovascular system, particularly in hypertension (1). The decrease in blood pressure induced by both Δ⁹-THC (22) and anandamide (23, 24) was larger and lasted longer in spontaneously hypertensive rats (SHRs) than in normotensive rats. These effects were primarily owing to decrease cardiac contractility and not to a reduction in peripheral resistance. When rimonabant was given to

anaesthetised SHRs, there was a marked and sustained increase in cardiac contractility and blood pressure (24). These findings lead to the suggestion that inhibitors of fatty acid amide hydrolase (FAAH) could play a role in the treatment of hypertension and cardiac hypertrophy (1), despite the fact that *in vivo* FAAH does not seem to degrade 2AG (1).

Unfortunately for our understanding but luckily for our patients, CB₁-receptor blockade using rimonabant was associated with a reduction in blood pressure comparable to that expected through weight loss in the RIO trials. The blood pressure reduction was especially important in obese hypertensive patients (see below). It is possible that in conditions such as obesity-associated hypertension, endocannabinoids, although increased, have lost their blood pressure lowering effect that is present in younger, healthier subjects. Thus, increased age and adiposity might be other key factors influencing the circulatory response to endocannabinoids. Unfortunately human data are lacking and even animal data have been obtained using mostly young, male, non-obese and non-hypertensive rodents. Further research on this is certainly needed.

The endocannabinoid system and the human cardiovascular system: novel experimental evidence

Increased visceral adiposity is regarded as the 'link' between overweight and cardiometabolic complications. A dysregulated, overstimulated ECS in visceral adipose tissue appears to significantly contribute to the cardiometabolic complications of visceral obesity (18–21). On this trail, we have recently obtained novel data supporting a relationship between the ECS and the human cardiovascular system. In an ongoing study on a large number of patients uninephrectomised for localised intracapsular carcinoma, renal samples from the spared portion of the kidney, as well as visceral and subcutaneous adipose tissue, were studied. Taking into consideration all the relevant anthropometric, metabolic and cardiovascular parameters of this non-diabetic population, we found that in patients with more advanced arteriolar damage (Fig. 1) – damage usually resulting from ageing and hypertension– CB₁ receptor gene expression was significantly increased in visceral perirenal adipose tissue (Fig. 2), even after correction for other variables such as blood pressure. These findings (Sarzani R., Bordicchia M, Marcucci P, Minardi D, Muzzonigro G, Mazzucchelli R, Montironi R, manuscript in preparation) suggest that an overactive ECS in visceral adipose tissue is related to vascular damage. Although an increase in circulating endocannabinoids has been documented (18–20), the most likely link between CB₁ overexpression in visceral adipose tissue and vascular damage is adiponectin, which is reduced in obesity but increases after CB₁ blockade (25). Rimonabant is also able to increase HDL cholesterol and reduce small, dense, oxidation-prone LDL (25), key mediators of vascular damage in large and small arteries. Nevertheless, despite decades of good research, our comprehension of the relationship between hypertension, lipid dysmetabolism and cardiovascular damage is far from clear. To the best of our knowledge, the first reported hypertension-related change in vascular gene expression was dramatic downregulation of an intracellular fatty acid binding protein (FABP), largely

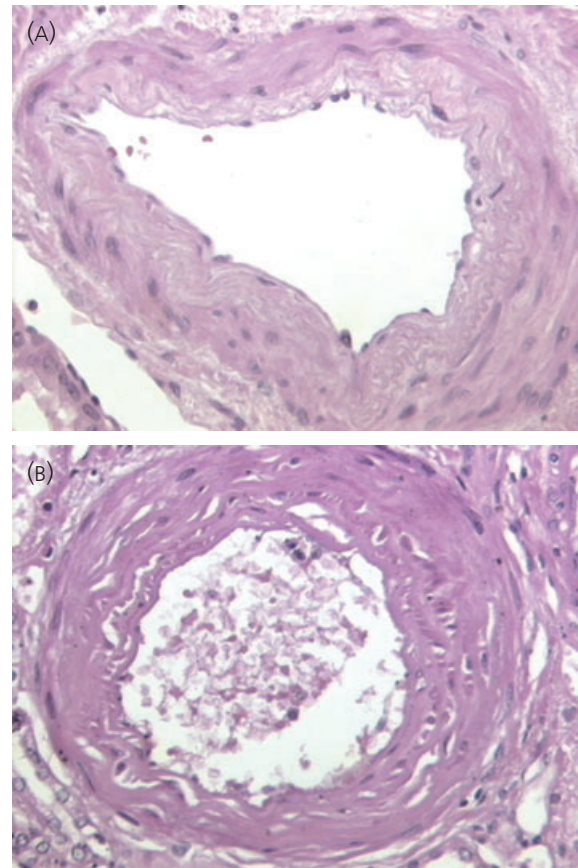


Fig. 1. Different degree of renal arteriolar damage in two different patients. (A) Intimal hyperplasia. (B) Severe hyperplasia and fibrosis. Scale, 200 \times .

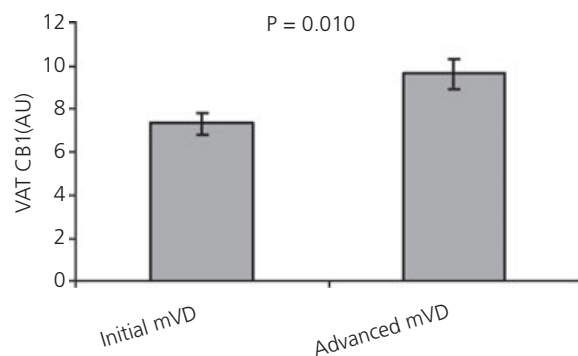


Fig. 2. CB₁ receptor gene expression in visceral adipose tissue (VAT) in patients with different severity of arteriolar microvascular damage. Significantly higher CB₁ gene expression was present in VAT of the patients with a more severe degree of renal microvascular damage.

expressed in aortic adventitial preadipocyte/adipocytes (26). The importance of the downregulation of FABP in hypertension remains unclear, but it is likely to reduce peripheral non-esterified fatty acids (NEFA) uptake and contribute to the rise in circulating NEFA levels that is often documented in hypertension, especially when associated with insulin resistance. Some NEFAs are also

endocannabinoids precursors and this appears to be a promising novel pathway to explore to understand the link between ECS and human hypertension.

The RIO trials

The best evidence to date on the cannabinoid system and the cardiovascular system in humans has come from the RIO trials; RIO-Lipids (25), RIO-Europe (27), RIO-North America (28) and RIO-Diabetes (29). In these trials, obese patients were treated with the rimonabant, which, at 20 mg (od) enhanced the loss of body weight more than lifestyle measures and with an improvement in metabolic parameter that exceeded that expected from weight loss by about 50% (25).

In the large number of obese patients studied, 20 mg rimonabant not only did not increase blood pressure (as expected from most animal studies) but blood pressure was reduced, reaching significance in RIO Lipids, RIO Diabetes, and in all RIO studies after meta-analysis (25, 29–31). Blood pressure reduction was seen in RIO Diabetes, despite the overall lower loss in body weight compared with the previous other three trials cited above (25, 27–29). More interestingly, considering only patients with high blood pressure at baseline (defined as $\geq 140/90$ mmHg for RIO Lipids, RIO North America and RIO Europe; $\geq 130/85$ mmHg for RIO Diabetes), the placebo-subtracted significant reduction in systolic and diastolic blood pressure was -2.5 and 2 mmHg, respectively (30, 31). These reductions are apparently small, but a fall of 2 mmHg systolic blood pressure translates to a 10% reduction in stroke mortality and 7% reduction in mortality for ischaemic heart disease (32). Although the RIO trials were not designed to study blood pressure variations, these findings are not only reassuring but also important for the overall cardiovascular benefits from CB₁ blockade. Indeed, together with the positive metabolic/dyslipidaemic results, it is clear that blocking cannabinoid effects mediated by the CB₁ receptor will result in an important reduction in cardiovascular risk in obese patients. Overall, it appears that Rimonabant behaves as a 'multiplier' of the many beneficial effects of body weight loss induced by a hypocaloric diet and increased physical activity.

Thus, the concept, based mostly on experimental results with *in vitro* or animal models, that CB₁-mediated endocannabinoid effects are beneficial to the cardiovascular system should be revised, at least in obese patients.

Conclusions

We are still very far from understanding the endocannabinoid system in humans, particularly with regard to the short- and long-term effects on the cardiovascular system. Thus, some answers will come from the publication of the results of longer-term clinical trials such as the STRADIVARIUS (Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant – the Intravascular Ultrasound Study; ClinicalTrials.gov Identifier: NCT00124332) trial, due for completion in August 2007, which tests whether the improvement in the cardiometabolic risk profile induced by rimonabant translates into changes within the coronary circulation. The enrolled patients with abdominal obesity, with metabolic syndrome

and/or smokers, have a documented 20–50% stenosis by coronary angiography. The volume of atheroma has also been assessed by intravascular ultrasound and by repeating coronary angiogram. The CRESCENDO trial (Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes; ClinicalTrials.gov Identifier: NCT00263042), which is still recruiting subjects and is ongoing, will help clarify the cardiovascular effects of long-term CB₁ blockade, because it will assess whether rimonabant reduces the risk of myocardial infarction, stroke and cardiovascular death in patients with abdominal obesity and with one coronary heart disease equivalent or two major risk factors for cardiovascular disease. Time (and much more work) will tell us much more about cannabinoids and the human heart.

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Conflicts of interest

The author has declared no conflicts of interest.

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