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CB_1 Cannabinoid Receptor Inhibition: Promising Approach for Heart Failure?

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Endocannabinoids are part of a novel signaling system, along with their cellular receptors and several proteins implicated in their synthesis, release, transport, and degradation. The endocannabinoids are endogenous lipid mediators generated by almost all cell types both in the brain and in the peripheral tissues, which have a wide range of biological effects similar to those of marijuana. 2-Arachidonoylglycerol and arachidonoyl ethanolamide (anandamide) are the 2 best characterized endocannabinoids. Their effects are mediated by 2 G protein–coupled receptors, CB_1 and CB_2, as well as additional, as-yet unidentified ones.[1] 2-Arachidonoylglycerol binds to both CB_2 and CB_1 receptors, whereas arachidonoyl ethanolamide has higher affinity for CB_1 receptors and may also bind to vanilloid VR_1 receptors. The tissue levels of endocannabinoids are determined by the balance between their biosynthesis (involving phospholipase D– and diacyl-glycerol lipase–dependent and other pathways), cellular uptake, and degradation by fatty acid amide hydrolase and/or monoacylglycerol lipases.[1,2] Both CB_2 and CB_1 receptors are negatively coupled to adenylate cyclase through $G_{i/o}$ proteins but can also signal via protein kinases A and C, mitogen-activated protein kinases, and cyclooxygenase 2 pathways, among others.[1,3] The CB_1 receptor is widely distributed in the central nervous system[1] and at lower levels in various peripheral tissues (eg, myocardium,[4–6] human coronary artery endothelial and smooth muscle cells,[7,8] adipose tissue,[9,10] and the liver[10–12]). Initially it was thought that CB_2 receptors were expressed only in immune and hematopoietic cells, but recent studies have also established their presence in the myocardium,[6] human coronary endothelial and smooth muscle cells,[7,8] brain,[13] and liver.[12] Modulation of the endocannabinoid system (ECS) may be therapeutically exploited in various cardiovascular (CV) disorders ranging from circulatory shock, stroke, atherosclerosis and restenosis, and hypertension, to cirrhotic cardiomyopathy, myocardial infarction, and chronic heart failure.[1,14,15]

CV Effects of Cannabinoids

In addition to their well-known psycho-active effects, cannabinoids and their endogenous and synthetic analogs exert a variety of CV effects. Δ^9-Tetrahydro-cannabinol (the active ingredient of marijuana, a mixed $CB_{1/2}$ agonist), HU-210 (a potent synthetic $CB_{1/2}$ agonist), and the endocannabinoid anandamide induce bradycardia, hypotension, and depressed cardiac contractility in anesthetized rodents. These effects are less pronounced/absent in conscious

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normotensive animals, but are augmented in hypertensive ones.[1] Short-term use of marijuana in humans usually causes tachycardia, whereas long-term use may lead to bradycardia and hypotension.[1] The mechanisms underlying the in vivo CV effects of endocannabinoids and their synthetic analogs are multifaceted, involving modulation of autonomic out-flow through sites of action at presynaptic autonomic nerve terminals and in the central nervous system, as well as direct effects on myocardium and the vasculature.[16] In the case of endocannabinoids, these effects are complicated by their rapid degradation to arachidonic acid that can be further metabolized into multiple vasoactive prostanoids.[1,14] CB_1 receptors in the myocardium mediate negative inotropy both in vitro and in vivo.[16] Cannabinoids can also elicit vasodilation through complex mechanisms (eg, CB_1- and vanilloid VR_1 receptor–dependent, NO-mediated or -independent, and endothelium-dependent or -independent).[14,16] The role of CB_2 receptors in the myocardium[6,17] is still elusive. Activation of CB_2 receptors in endothelial and inflammatory cells attenuates tumor necrosis factor α (TNF-α)–induced endothelial inflammatory response, chemotaxis, and adhesion of inflammatory cells to the activated endothelium, and consequent release of various proinflammatory mediators (key processes involved in the initiation and progression of atherosclerosis, restenosis, and reperfusion injury)[15,18] and smooth muscle proliferation.[8]

Despite the above-mentioned multiple CV effects of endocannabinoids, the ECS appears to play a limited role in CV regulation under normal physiologic conditions. However, in various pathologic states (eg, in shock, cardiomyopathy, and heart failure), the ECS may become overactivated, thereby contributing to hypotension/cardiodepression through CV CB_1 receptors. Paradoxically, the ECS may also be activated as a compensatory mechanism in various forms of hypertension to limit pathologically increased blood pressure and myocardial contractility.[1] In this case, the enhancement of endogenous cannabinoid tone by inhibition of the anandamide-degrading enzyme fatty acid amide hydrolase can decrease blood pressure and myocardial contractility,[1] but a detailed discussion of this is beyond the scope of this brief synopsis.

In addition to the above-mentioned hemodynamic effects, CB_1 receptor activation contributes to the development of CV risk factors associated with obesity/metabolic syndrome and diabetes (abdominal obesity, plasma lipid alterations, insulin and leptin resistance) in humans[19–24] through mechanisms that have not yet been fully explored. Accordingly, a number of CB_1 receptor inverse agonists/antagonists (rimonabant, taranabant, surinabant, otenabant, and AVE-1625) are now in clinical development/trials for obesity and its cardiometabolic consequences (Figure 1). The results of several clinical studies involving the CB_1 antagonist lead compound rimonabant (SR141716A) are now available.[19–25]

In this review we will briefly discuss the accumulating evidence from both preclinical and clinical studies forecasting potential benefits of CB_1 receptor inverse agonists/antagonists such as rimonabant in patients with heart failure.

Chronic Heart Failure: A Multifaceted Disorder

Chronic heart failure (CHF) is a leading cause of hospitalization, morbidity, and mortality worldwide. A variety of patho-physiologic conditions such as acute and chronic ischemic heart disease resulting from altered coronary artery circulation or infarction, cardiomyopathies, myocarditis, pressure overload and defects in genes encoding contractile apparatus, intercellular matrix, and cytoskeleton or mitochondrial proteins eventually lead to impaired myocardial function.[26,27] The progression of CV dysfunction to heart failure is multifaceted and may involve activation of a variety of secondary pathways (neuropeptides, neurohormones, inflammatory cytokines, inducible nitric oxide synthase, oxidative/nitrosative stress, matrix metalloproteinases, and the nuclear enzyme poly[ADP-ribose] polymerase), eventually leading

to abnormalities in various signaling processes and cardiac receptors, calcium homeostasis, and contractile protein desensitization. Other key features include structural alterations such as cardiac and vascular remodeling with hypertrophy, fibrosis, and cardiac dilation and necrosis.[26–28] Accumulating preclinical and clinical evidence suggests that inflammation and oxidative/nitrosative stress are important in the progression of many forms of heart failure, and the clinical value of various biomarkers of inflammation and oxidative/nitrosative stress is being intensively investigated in patients with CHF.[27]

CB_1 Antagonists for Heart Failure: Possible Beneficial Effects, Mechanisms

The profound CB_1-mediated hypotensive and cardiodepressive response (discussed above) have strongly suggested a role for endocannabinoids in hypotensive states. In fact, activation of the ECS has been implicated in CV collapse in hemorrhagic, septic, and cardiogenic shock and advanced liver cirrhosis.[1] In these conditions, overproduction of endocannabinoids triggered by bacterial endotoxin has been documented in activated macrophages and platelets, whereas treatment with CB_1 antagonists prevented or reversed the hypotension and/or decreased myocardial contractility.[1,18]

Previous studies using rat models of acute and chronic myocardial infarction with CB_1 agonists/antagonists yielded conflicting results.[29,30] The CB_1 antagonist AM251 was suggested to promote cardiac remodeling in a chronic heart failure study, but counterintuitively it tended to improve hemodynamics and survival. Treatment with the agonist HU210 was shown to prevent endothelial dysfunction, but at the same time it increased left ventricular end-diastolic pressure, a negative effect. A major limitation of the above studies is the use of a high dose of HU210, which was previously reported to cause severe psychotropic side effects and hypothermia and to exert antiarrhythmic and anti-inflammatory effects. In addition, it was found to decrease myocardial damage in perfused hearts by mechanisms not related to CB_1 activation, which complicates the interpretation of the results. Other confounding factors are the large variations in the experimental models used and the suboptimal dose of the CB_1 antagonist AM251 (other studies reporting anti-inflammatory and cyto-protective effects of CB_1 antagonists have used at least an order of magnitude higher dose of these drugs).

More recently we have explored the role of ECS in a well-established mouse model of doxorubicin-induced heart failure.[6] Doxorubicin is one of the most effective antitumor agents available for treatment of a variety of solid tumors and hematologic malignancies; however, its clinical use is limited because of the risk of severe cardiotoxicity. The pathophysiology of doxorubicin-induced cardiotoxicity in this mouse model of acute cardiomyopathy/heart failure is complex, since it involves oxidative/nitrosative stress, activation of various mitogen-activated protein kinases and inflammatory pathways, dysregulation of iron and intracellular Ca^{2+} homeostasis/contractile proteins, alterations in mitochondrial respiratory chain function and β-adrenergic receptor signaling, and cell death. Therefore, this heart failure model allows one to study the interplay between various signaling pathways involved in cell survival and cell death, which is applicable to many forms of cardiac disease, including CHF. Doxorubicin administration was associated with severe depression of left ventricular systolic pressure, maximum first derivative of ventricular pressure with respect to time (+dP/dt), stroke work, ejection fraction, cardiac output, and load-independent indices of left ventricular contractility (end-systolic pressure-volume relation, preload-recruitable stroke work, dP/dt–end-diastolic volume relation) in mice.[6] Tissue anandamide content, but not CB_1/CB_2 receptor expression, was elevated in the myocardium after doxorubicin administration and also in cardiomyocytes exposed to doxorubicin in vitro, suggesting activation of the ECS. The most likely trigger of increased endocannabinoid production/decreased degradation in this model is the increased oxidative/nitrosative stress, which is similar to that reported to develop in ischemia/reperfusion injury.[18]

Pretreatment of mice with CB_1 antagonists (rimonabant and AM281) not only improved doxorubicin-induced cardiac dysfunction, but also attenuated the doxorubicin-induced cell death both in vivo and in vitro. This cytoprotective effect is particularly important because it suggests that the cardioprotective effect of CB_1 antagonists in various pathologies may extend beyond hemodynamics. It is tempting to speculate that this beneficial effect may involve attenuation of the oxidative/nitrosative stress and inflammation and interrelated signaling pathways (key triggers of doxorubicin-induced cell death in cardiomyocytes and endothelial cells). Indeed, CB_1 antagonists appear to exert potent anti-inflammatory and cytoprotective effects in multiple preclinical disease models.[31–37] More important, rimonabant attenuates multiple inflammatory markers (eg, TNF-α and C-reactive protein), plasma leptin and insulin levels, and increases plasma adiponectin in obese patients with the metabolic syndrome and/or type 2 diabetes.[19–24]

Effects of CB_1 Inhibition on Cardiometabolic Risk

Chronic treatment with the CB_1 receptor antagonist rimonabant in rodent models of diet-induced obesity has suggested direct effects on peripheral fat metabolism, since the observed transiently reduced food intake was accompanied by sustained weight loss.[1,38,39] CB_1 receptor activation in adipocytes and hepatocytes increases lipogenesis and decreased fatty acid oxidation in adipose tissue[9] and in the liver.[11] Consequently, CB_1 blockade can reverse the increased adiposity and hepatic steatosis.[31] CB_1 blockade also improves glucose tolerance, insulin and leptin sensitivity, and the plasma lipid profile in diet-induced or genetically obese animals.[40]

In multicenter clinical trials conducted in obese individuals with the metabolic syndrome and/or type 2 diabetes, rimonabant reduced body weight and waist circumference and exerted additional beneficial effects such as improved glucose tolerance and dys-lipidemia (reduced triglyceride and increased high-density lipoprotein cholesterol levels), attenuation of plasma leptin and insulin levels and inflammatory markers, and increased plasma adiponectin.[19–24] These favorable effects of rimonabant were only partially weight loss–dependent, further implying a direct effect of the ECS on various hormonal/metabolic parameters.[19–24] On the basis of these studies it was also suggested that rimonabant may have favorable effects in atherosclerosis. With this in mind, the results of the recent Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant: The Intravascular Ultrasound Study (STRADIVARIUS)[25] examining the effect of 18 months of rimonabant treatment on coronary disease progression in patients with abdominal obesity/metabolic syndrome yielded somewhat disappointing results.[25] Rimonabant had no significant effect on the primary end point of coronary disease progression, the percent atheroma volume; however, it decreased the normalized total atheroma volume, which was the secondary end point.[25] The favorable effects of rimonabant on body weight and hormonal/metabolic parameters were similar to those observed in the previous large-scale trials.

Side Effects of CB_1 Antagonists, Concerns

Rimonabant, the first CB_1 antagonist, successfully completed 5 phase III trials[19–22,25] and is currently on the market in the European Union and in several other countries for the treatment of obesity and associated cardiometabolic risk. It was generally well tolerated and caused only a slightly higher incidence of the signs of depressive mode disorder (from 1.6% to 3.2% according to data pooled from the 4 Rimonabant in Obesity [RIO] studies[23]), nausea and dizziness, and diarrhea compared with placebo.[19–24] The increased incidence of psychiatric side effects of rimonabant, however, was largely responsible for a US Food and Drug Administration advisory panel that rejected approval for rimonabant's use in the United States in 2007. In the follow-up STRADIVARIUS trial, which did not exclude patients with

preexisting anxiety and depressive disorder, the higher incidence of psychiatric adverse events in patients treated with rimonabant was confirmed compared with placebo, although the incidence of serious adverse events such as attempted or completed suicide was low and statistically not different from placebo.[25] This issue will undoubtedly be further explored by ongoing and future studies.

Conclusions, Future Perspectives

The above-discussed studies strongly suggest that the beneficial effects of CB_1 antagonists in various cardiomyopathies on contractile function may extend far beyond the simple inhibition of CB_1-mediated CV depressive effects of pathologically overproduced endocannabinoids in these disease conditions. Future studies using both knockout mice and additional $CB_{1/2}$ agonists/antagonists are warranted to explore the possible interactions of ECS with oxidative/nitrosative stress and related inflammatory pathways. The beneficial effects of CB_1 inhibition in cardiomyopathies coupled with accumulating evidence that rimonabant decreases cardiometabolic risk factors in both patients and animal models of obesity and metabolic disorders (including inflammatory markers such as TNF-α and C-reactive protein, which are also important prognostic markers in human heart failure) is particularly encouraging from a therapeutic point of view (Figure 2). Further prospective studies should also examine whether CB_1-antagonist treatment leads to reduction of clinical events related to coronary disease. The insulin-sensitizing action of rimonabant should also be further exploited with possible additional benefits in some patients with heart failure. Novel therapeutic strategies targeting development of peripherally restricted CB_1 antagonist may improve the bene- fit/risk ratio for this class of compounds by decreasing psychiatric side effects.

Taking the clinical data together with the body of preclinical data as a whole, one can assume that pharmacologic inhibition of CB_1 receptors with rimonabant (and possibly other CB_1 antagonists) may provide significant benefits in multiple CV diseases, forecasting potential benefits in patients with CHF. As additional CB_1 inhibitors enter clinical stage testing, one can hope that the body of direct human clinical and mechanistic data on the pathophysiologic role of ECS in CV disease and CHF will increase.

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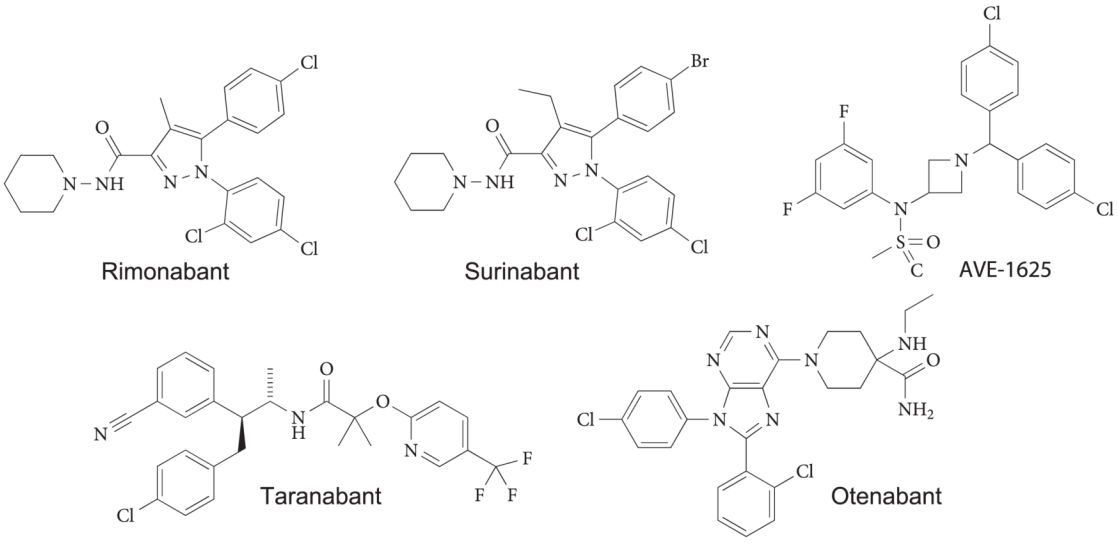

Figure 1.
Chemical structure of various CB_1 cannabinoid receptor inverse agonists/antagonists in clinical development.

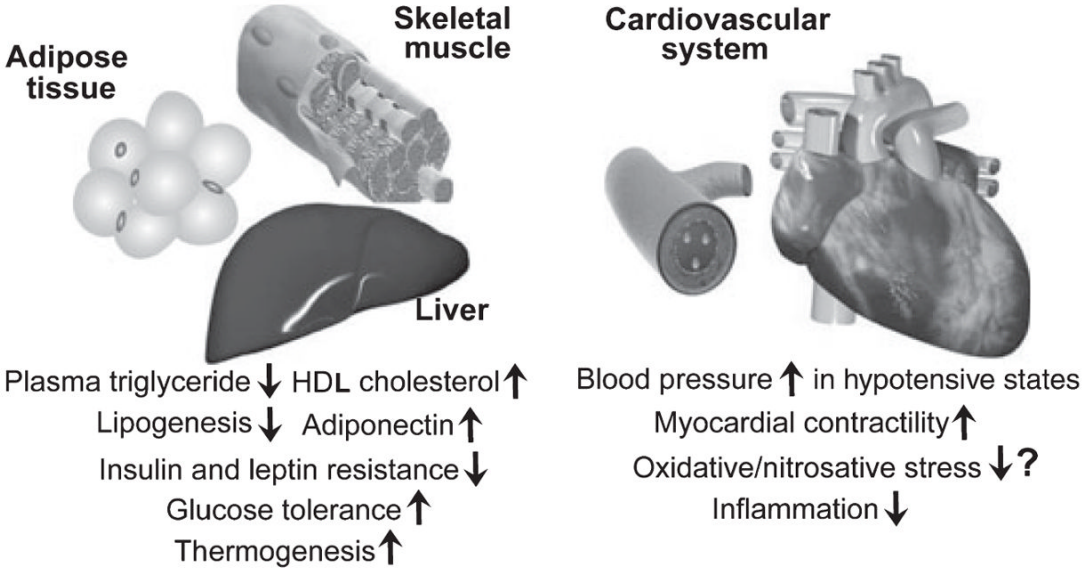

Figure 2.
Favorable effects of rimonabant from preclinical and clinical studies forecasting possible benefits in the treatment of chronic heart failure. HDL indicates high-density lipoprotein; ↓decrease; ↑increase.