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THE ENDOCANNABINOID SYSTEM AND CARDIOVASCULAR DISEASE

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Introduction

Cannabinoids and their endogenous and synthetic analogs exert complex cardiovascular effects both *in vitro* and *in vivo* mediated by cannabinoid receptor-dependent and -independent mechanisms. The cannabinoid CB1 and CB2 receptors and the endocannabinoid degrading enzymes are expressed in the myocardium [1-3], human coronary artery endothelial and smooth muscle cells [4, 5], and infiltrating inflammatory cells, among many other tissues/cells [6]. In experimental animals and in humans (depending on the route of administration, duration, and the dose) these cardiovascular effects may include CB1-mediated bradycardia/tachycardia, hypotension, and depressed cardiac contractility involving modulation of autonomic outflow 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 [7]. In spite of the above mentioned cardiovascular effects of endocannabinoids, the endocannabinoid system (ECS) appears to play a limited role in cardiovascular regulation under normal physiological conditions. However, in various disease conditions, the ECS may become overactivated and play important protective and/or detrimental roles.

Key Points

- The cannabinoid CB1 and CB2 receptors and endocannabinoid degrading enzymes are present in cardiovascular tissues.
- Activation of cardiovascular CB1 receptors leads to hypotension and decreased cardiac contractility. However, the role of myocardial CB2 receptors is still elusive.
- The ECS plays a limited role in cardiovascular regulation under normal physiological conditions.
- In various forms of shock and heart failure, the ECS may become overactivated and contribute to depressed cardiovascular function, which can be prevented or attenuated by CB1 antagonists.
- The ECS may also be activated as a compensatory mechanism in various forms of hypertension to limit pathologically increased blood pressure and myocardial contractility.
- CB1 antagonists exert various cytoprotective and anti-inflammatory effects in multiple unrelated preclinical disease models and also in patients with obesity and/or metabolic syndrome.
- Activation of CB2 receptors in inflammatory cells and endothelium attenuates TNF-α-induced endothelial inflammatory response, chemotaxis, and adhesion of inflammatory cells to the activated endothelium, and consequent release of various proinflammatory mediators, which may underlie the beneficial effects of CB2 agonists in vascular inflammation, atherosclerosis, and myocardial ischemia/reperfusion injury.

State of the Art

Activation of the ECS in inflammatory cells and cardiovascular tissues by bacterial endotoxin(s) has been implicated in cardiovascular collapse in various forms of shock (e.g., septic, hemorrhagic, and cardiogenic) and advanced liver cirrhosis (reviewed in [6]). In these conditions, treatment with CB1 antagonists prevented or reversed the hypotension and/or decreased myocardial contractility (reviewed in [6, 8]). In rat models of acute and chronic myocardial infarction, studies with CB1 agonists/antagonists yielded conflicting results [9, 10]. More recently, the role of the ECS was explored in a mouse model of doxorubicin(DOX)-induced heart failure [3]. Following doxorubicin administration, the tissue anandamide content, but not CB1/CB2 receptor expression, was elevated in the myocardium and also in cardiomyocytes exposed to DOX *in vitro*, suggesting activation of the ECS. Pretreatment of mice with CB1 antagonists (rimonabant and AM281) not only improved DOX-induced cardiac dysfunction, but also attenuated the DOX-induced cell death both *in vivo* and *in vitro*. This cytoprotective effect suggests that the cardioprotective effect of CB1 antagonists in various cardiac pathologies may extend beyond beneficial hemodynamic effects. In fact, CB1 antagonists exert various anti-inflammatory and cytoprotective effects in multiple unrelated preclinical disease models [11-17]. Furthermore, rimonabant also attenuates multiple inflammatory markers [e.g., tumor necrosis factor-α (TNF-α), C-reactive protein, etc.], plasma leptin and insulin levels, and increases plasma adiponectin in obese patients with metabolic syndrome and/or type 2 diabetes, thereby attenuating the development of cardiovascular risk factors associated with obesity/metabolic syndrome and diabetes [18-24]. On the basis of these studies, it was also suggested that rimonabant may have favourable effects in atherosclerosis. With this in mind, the results of the recent STRADIVARIUS clinical trial examining the effect of 18 months of rimonabant treatment on coronary disease progression in subjects with abdominal obesity/metabolic syndrome yielded somewhat disappointing results [19]. Rimonabant had no significant effect on the primary endpoint of coronary disease progression (the percent atheroma volume), however, it decreased the normalized total atheroma volume, which was the secondary endpoint [19]. The favourable effects of rimonabant on body weight and hormonal/metabolic parameters were similar to those observed in previous large-scale trials.

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 [6]. In this case, the enhancement of endogenous cannabinoid tone by inhibition of the anandamide degrading enzyme fatty acid amide hydrolase (FAAH) can decrease blood pressure and myocardial contractility [6].

The role of myocardial CB2 receptors during ischemia/reperfusion and other cardiovascular pathologies is still vague. In contrast, activation of CB2 receptors in inflammatory cells and endothelium attenuates 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) [8, 25]. Activation of CB2 receptors in human coronary smooth muscle cells

decreases proliferation [5], which may have clinical implications for the treatment of atherosclerosis and restenosis.

Priorities for Future Studies

An increasing number of studies suggests that the beneficial effects of CB1 antagonists in various cardiomyopathies on contractile function may extend far beyond the simple inhibition of CB1-mediated cardiovascular depressive effects of pathologically overproduced endocannabinoids in these disease conditions. Future studies using both knockout mice and additional selective CB1/2 agonists/antagonists must explore the possible interactions of the ECS with oxidative/nitrosative stress and related inflammatory pathways in models of myocardial ischemia/reperfusion, cardiomyopathies, heart failure, and atherosclerosis. Additional prospective studies should also examine if CB1 antagonist treatment leads to reduction of clinical events related to coronary disease. Novel therapeutic strategies targeting development of peripherally restricted CB1 antagonists may improve the benefit/risk ratio for this class of compounds by decreasing psychiatric side effects.

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