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Cannabinoid CB1/CB2 Receptors in the Heart: Expression, Regulation, and Function

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Abstract

Endocannabinoids exert their actions in the heart and vessels, at least in part, by stimulating the cannabinoid CB1 and the CB2 receptor subtypes which belong to a group of seven transmembrane-spanning receptors and are coupled to Gi/o-proteins. Activation of cardiovascular CB1 receptors leads to depressed cardiac contractility and hypotension. Conversely, in most studies, the CB1 receptor antagonists are cardioprotective against ischemia–reperfusion injury, myocardial ischemia, heart failure, and cardiomyopathies. Evidence to date indicates that CB2 receptor activation is cardioprotective. CB2 receptor-mediated effects such as anti-inflammation and anti-fibrosis may be in part opposite to the actions of the CB1 receptor. The aim of this review is to up-date on recent experimental findings and controversies on the role of endocannabinoid system in the myocardial injury with emphasis on pathophysiological processes such as left ventricular remodeling, cardiac fibrosis, hypertrophy, and endothelial dysfunction. Recent experimental studies employing genetic deficiency of CB1 and CB2 receptors and endocannabinoid anandamide metabolizing enzymes are reviewed. Moreover, the protective mechanisms which are mediated by cannabinoid receptors during ischemic preconditioning as well as in the early and late phase after myocardial infarction are discussed in the context of possible therapeutic implications.

Keywords: cannabinoid receptors, CB1, CB2, heart, myocardial infarction, heart remodeling

1. Introduction

Endocannabinoids, its degrading enzymes and the cannabinoid CB1 and CB2 receptors are present in rodent and human cardiovascular tissues. In addition to its role in the control of the

central nervous system, the endocannabinoid system (ECS) may play a pivotal part in cardiovascular regulation by heart diseases (reviewed in [1-3]).

In normal physiological conditions, ECS is not highly regulated. However, by cardiovascular pathologies, this system is activated and may reflect a protective response which limits cardiac injury. Activated ECS has been implicated in acute cardiovascular conditions such as hemorrhagic, septic, and cardiogenic shock as well as in chronic diseases such as coronary heart disease, heart failure, and cardiomyopathy.

Endocannabinoids exert their actions in the heart and vessels, at least in part, by stimulating the cannabinoid CB1 and the CB2 receptor subtypes which belong to a group of seven transmembrane-spanning receptors and are coupled to Gi/o-proteins [4, 5]. Signaling through the CB1 receptor elicits hypotension, bradycardia, and negative inotropy [6]. Moreover, this receptor subtype is implicated in inflammation, apoptosis, oxidative stress [7], and metabolic dysregulation [8], thereby contributing to tissue injury. The CB2 receptors, on the contrary, may play a compensatory anti-inflammatory, anti-oxidative, and anti-atherogenic role [9, 10] contributing to cardiovascular protection.

Nevertheless, the role of cannabinoid receptors in the heart under several pathological conditions remains controversial. Recent studies on hemodynamic, antiarrhythmic, and cardiometabolic effects of cannabinoids have been highlighted in several excellent reviews [2, 3, 11-14]. Hence, these topics are not in the scope of this chapter.

The aim of this review was to up-date on recent findings and controversies on the role of ECS in the myocardial injury with emphasis on pathophysiological processes such as left ventricular remodeling, cardiac fibrosis, hypertrophy, and endothelial dysfunction. Starting with the localization of the cannabinoid system components in the heart under normal and pathological conditions, the role of both CB1/CB2 receptors in the regulation of the cardiac function will be analyzed. Experimental studies in mice deficient in cannabinoid receptors and endocannabinoid anandamide metabolizing enzymes greatly expanded our knowledge on the role of ECS. Hence, lessons from these studies will also be discussed. Moreover, the protective mechanisms which are mediated by cannabinoid receptors during ischemic preconditioning as well as in the early and late phase after myocardial infarction will be described in the context of possible therapeutic implications.

2. Endocannabinoids and cannabinoid receptors in the heart

The major endocannabinoids, anandamide, and 2-arachidonoylglycerol (2-AG) have been detected in the rat heart by Schmid et al. [15]. These findings were later confirmed by Wagner et al. [16] who also revealed the presence of CB1 receptors via immunohistochemistry in isolated rat hearts. Finally, the presence of both CB1 and CB2 receptors has been confirmed in myocardium of rat [17, 18], mice [19], and guinea pigs [20]. Messenger RNA and immunoreactivity for CB1 receptors have also been reported from murine cardiomyocytes [21], and only one receptor subtype, CB1, was present on neonatal cardiomyocytes [22].

In human heart, CB1 mRNA expression has been first found by Galiegue et al. [23] and later confirmed in isolated human atrial muscle on the protein level by Bonz et al. [24]. Moreover, human primary cardiomyocytes [9] and coronary vascular smooth muscle [25] also expressed CB1 receptors. Finally, it has been recently demonstrated that mRNA transcripts of CB1 and CB2 receptors are expressed in an almost equal proportion on healthy human left ventricular myocardium [26].

Hence, the main components of the ECS are present in rodent and human healthy heart. Their regulation under pathophysiological conditions has been intensively investigated during the last decade in different models of cardiac injury and in human diseases.

To begin with, circulating levels of endocannabinoids were elevated after cardiac injury, such as **myocardial infarction** in the rat [27] and **ischemia/reperfusion** in mice [28]. The CB2 receptors were upregulated in ischemic cardiomyocytes [28] and in cardiomyocytes following cultivation under hypoxia [29]. Our group found general induction of CB1 and CB2 receptor gene expression due to experimental myocardial infarction in the rat 6 weeks after operation [30].

Interestingly, in **heart failure** induced by doxorubicin, tissue anandamide content was elevated, whereas the expression of CB1/CB2 receptors in the heart was not changed [21]. Also **diabetic cardiomyopathy** in mice was characterized by increased myocardial endocannabinoid anandamide levels, although in this model, the CB1 receptors were upregulated parallel to increased oxidative/nitrative stress and activation of *p38* [31].

In humans, the endocannabinoid 2-AG level elevated in the infarct-side coronary artery of **acute myocardial infarction** patients along with increased reactive oxygen species and *tumor necrosis factor- α* levels [19]. Furthermore, elevated endocannabinoid plasma levels have been associated with coronary circulatory dysfunction in human obesity [32].

Aortic stenosis patients, who are known to develop heart hypertrophy, have significantly higher concentration of anandamide, its degrading enzyme fatty acid amide hydrolase (*FAAH*) and expression of CB2 receptors, which are predominantly located on cardiomyocytes [33]. Similarly, in patients suffering from **heart failure**, peripheral blood levels of endocannabinoids were elevated, whereas the expression of CB1 receptors was downregulated 0.7-fold and CB2 receptors was upregulated more than 11-fold indicating a shift toward CB2 expression [26].

Recently, in **human epicardial adipose tissue**, expression of the CB1/CB2 receptors and *FAAH* content was compared between patients with and without ischemic heart disease [34]. In ischemic hearts, the CB1-to-CB2 expression ratio shifted toward CB1 and was accompanied by higher *PKA* activation. In contrast, in nonischemics, *CB2*, *FAAH*, *PLC*, and *PKC* as well as *ERK1/2* were increased.

Concerning intracellular localization of the cannabinoid receptors, evidence is now provided for CB1 receptors. They were found in specific restricted regions within cardiac myocytes as demonstrated by array tomography in mice heart tissues [35]. Moreover, Currie et al. [36] suggested the existence of cardiac nuclear CB receptors.

Altogether, endocannabinoids and both CB1/CB2 receptors are present in human and murine hearts. The receptors co-localize with cardiac myocytes, coronary vascular smooth muscle, and endothelial cells as well as with epicardial adipose tissues.

Increased circulating and myocardial endocannabinoids levels as well as regulation of CB1 and CB2 receptors in heart diseases may reflect a protective response of the local ECS to limit cardiac injury. Whereas the CB1 receptors expression levels are controversially regulated depending on the heart disease model and cardiac function, the CB2 receptors are mostly upregulated. Thus, the endocannabinoid—CB2 receptor protective axis may play a major role in limiting injury.

3. Cardiac function

In healthy individuals, activation of ECS does not significantly regulate cardiac functions. In the intact heart of rodents, endogenous CB1/CB2 receptor agonists are also not involved in the electrophysiological processes and cardiac rhythm regulation [37]. Conversely, CB1 receptor antagonists do not affect cardiac hemodynamic in normotensive rodents [6, 30].

As previously described, in cardiac disorders and after myocardial infarction, circulating levels of endocannabinoids are elevated and the majority of studies suggest that this elevation improves cardiac performance [3, 27].

However, administration of anandamide, D9-tetrahydrocannabinol (Δ -9-THC), or synthetic cannabinoids causes complex hemodynamic changes and changes in heart rate and contractility [6]. Moreover, there are reports of adverse cardiovascular effects following cannabis or synthetic cannabinoid use, including myocardial infarction, arrhythmias, and sudden death [38, 39]. These negative effects may be related to increased sympathetic activity and inhibition of parasympathetic activity, leading to tachycardia, increased oxygen demand, and arrhythmias [40].

Regulation of cardiac contractility by the cannabinoid system is complex and includes actions on the nervous system and local cardiac mechanisms.

It has been previously assumed that cardiovascular effects of cannabinoids were centrally mediated through activation of receptors in the brain. However, evidence from studies mentioned below suggests that most effects are mediated locally through cardiac cannabinoid receptors. The activation of presynaptic CB1 receptors might decrease the release of noradrenalin contributing to negative inotropy [41]. Albeit, in some studies, effects on cardiac contractility were independent of the endogenous noradrenalin release [42]. Other possible mechanisms of negative inotropic effects include inhibition of voltage-dependent Na^+ and L-type Ca^{2+} channels in myocytes [43] and suppression of $\text{Na}^+/\text{Ca}^{2+}$ exchanger current [44, 45].

It is now becoming clear that negative inotropy is mediated through the CB1 receptor. This has been shown in papillary muscles, isolated hearts, and in rodent *in vivo* models [6]. Conversely, our group observed that an inhibition of CB1 receptors with rimonabant increased heart inotropy in rats after myocardial infarction but not in healthy rats. This im-

plies chronic activation of the endocannabinoid system after cardiac ischemia [30]. In this study, where hemodynamic parameters were measured 6 weeks after myocardial infarction using heart catheter, the CB1 receptor antagonist rimonabant significantly increased maximal and minimal peak rate of left ventricular pressure increase (dP/dt_{\max} and dP/dt_{\min}), preventing a decrease in contractility post myocardial infarction. Moreover, in the rat model of metabolic syndrome, the CB1 receptor blockade also improved systolic cardiac function raising fractional shortening and ejection fraction [30]. The positive inotropic effect of CB1 antagonism in these studies was associated with increased cardiac protein expression of *sarcoplasmic reticulum Ca²⁺ATPase (SERCA2a)* which is known to raise intracellular calcium concentration.

In contrast to CB1 receptor activation, CB2 receptor activation does not modulate the ion channel function (reviewed in [46]). Hence, it is not pronounced that the CB2 receptor mediates contractility effects. However, in one study, CB2 receptors developed positive contractile response in rat isolated atria associated with increased *cAMP* production [42].

Given that endocannabinoids are cleaved by hydrolysis as well as cyclooxygenase-2, lipoxygenases, and cytochrom P450-mediated oxidative metabolism, the generated autacoids may exert additional cardiovascular effects [6]. This fact requires further investigations.

4. Lessons from knockout mice

4.1. CB1 receptor knockout mice (*CB1^{-/-}*)

The generation of mice deficient in CB1 or CB2 receptors has greatly expanded our knowledge on the role of these receptor subtypes in heart disease.

In *CB1^{-/-}* mice, basal blood pressure and heart rate are normal [47]. Compared with wild type, CB1 knockouts showed a marked increase of mortality due to acute [48] and chronic heart failure [49] after pressure overload due to transverse aortic constriction. Moreover, in the late period after aortic constriction, compared to wild-type mice, *CB1^{-/-}* mice had significantly worse cardiac functional parameters associated with the activation of the *epidermal growth factor* receptor and *mitogen-activated protein kinases P38* and *ERK*. These findings suggest a protective role of the CB1 receptor stimulation in the heart [49].

On the other hand, genetic deletion of the CB1 receptor attenuated the diabetes-induced cardiac dysfunction [31]. Moreover, this study suggests that over-activation of this receptor subtype may play an important role in the pathogenesis of diabetic cardiomyopathy by facilitating angiotensin AT1 receptor signaling, *MAPK* activation, oxidative/nitrative stress, inflammation, cell death, fibrosis, and contractile dysfunction. Conversely, CB1 receptor inhibition may be of significant benefit in the treatment of diabetic cardiovascular complications.

In summary, there are controversies concerning the role of the CB1 receptor activation in cardiac pathology: It may be both deleterious and beneficial depending on the disease model. By over-activation of this receptor, the pathological reactions may be provoked.

4.2. CB2 receptor knockout mice ($CB2^{-/-}$)

In the $CB2^{-/-}$ mice, initially, an absence of immunomodulatory effects of endocannabinoids was observed [50, 51]. Later, Defer et al. [52] showed the importance of the CB2 receptor in cardioprotection. In the infarction/reperfusion model in $CB2^{-/-}$ mice, increased infarct size was associated with enhanced apoptosis and remodeling. Moreover, in the late remodeling phase after myocardial infarction, $CB2^{-/-}$ mice developed left ventricular dysfunction, exacerbated fibrosis, and dilative cardiomyopathy [52].

The role of the CB2 receptor during the initial phase of **ischemic cardiomyopathy** development prior to the onset of ventricular dysfunction or infarction has been studied in the $CB2^{-/-}$ mice by repetitive periods of ischemia/reperfusion [53]. $CB2^{-/-}$ mice showed an increased rate of apoptosis, irreversible loss of cardiomyocytes, persistent left ventricular dysfunction, increased inflammatory response, and decreased anti-oxidative capacity 60 days after the injury.

Further studies of remodeling processes in reperfusion infarction in the $CB2^{-/-}$ mice again confirmed the cardioprotective role of this receptor subtype [54]. In contrast to a rapid formation of granulation tissue and a compacted non-transmural scar in wild-type mice after 7 days of reperfusion, $CB2^{-/-}$ mice showed a non-compacted transmural scar and a significantly worse cardiac function. Adverse myocardial remodeling in $CB2^{-/-}$ mice has been associated with macrophage infiltration and low induction of tenascin C, collagen-1 α , or lysyl oxidase [54].

Hence, it seems that the CB2 receptor is implicated in multiple pathophysiological processes after heart injury: It modulates inflammatory response, collagen deposition, and organization of stable scar during remodeling.

4.3. Fatty acid amide hydrolase knockout mice ($FAAH^{-/-}$)

Inhibition of the endocannabinoid anandamide metabolizing enzyme, the fatty acid amide hydrolase ($FAAH$), is another strategy to study the impact of endocannabinoid system in health and disease. $FAAH^{-/-}$ mice had a normal hemodynamic profile, despite of 2.5-fold increase in the myocardial anandamide levels [55]. Albeit by aging, these mice exhibit less cardiac dysfunction, decreased levels of oxidative stress, and inflammation compared to the wild type [56]. Thus, an increased endocannabinoid activity by aging could be beneficial in the context of anti-inflammatory and anti-atherosclerotic effects.

However, in the doxorubicin model of heart failure, $FAAH^{-/-}$ mice compared to their wild type were characterized by increased mortality due to cardiac dysfunction and myocardial oxidative-nitrative stress [57]. This study suggests that in heart failure model associated with mitochondrial dysfunction and ROS generation, $FAAH$ plays a key role in controlling the anandamide-induced myocardial cell death. Moreover, this cardiac injury was, at least in part, mediated by the activation of CB1 receptors by endocannabinoids, since these effects could be attenuated by selective CB1 antagonists [57].

5. Ischemia–reperfusion injury

Short ischemia/reperfusion episodes—known as ischemic preconditioning—protect the myocardium against infarction [58]. This endogenous cardioprotective mechanism could be experimentally activated at two time points: The early preconditioning when the treatment is applied 1–4 h before ischemia and the delayed preconditioning when the treatment is applied 24–72 h before induction of myocardial infarction. Importantly, endogenous cannabinoid 2-AG is increased by preconditioning in the heart [59].

Initial studies on the role of cannabinoids in cardiac ischemia were predominantly performed *ex vivo* in papillary muscles or isolated heart. In these models, endocannabinoids ameliorated ischemia/reperfusion injury and reduced the early phase of heart remodeling (reviewed in [13, 60, 61]). It also has been pointed at the role of CB2 receptor activation in remote ischemic preconditioning [62–65]. Albeit, Underdown et al. [66] suggested that anandamide reduced infarct size in rat isolated hearts by interaction with a new cannabinoid receptor subtype, distinct from CB1 or CB2 receptors.

Further studies, which aimed to elucidate the role of CB1/2 receptors in the heart, were performed in the animal model of myocardial infarction via ligation of the left coronary artery. Most investigations used an indirect approach by blocking the beneficial effects of endocannabinoids activation either by CB1 or CB2 receptor antagonists.

In the rat model of coronary occlusion/reperfusion, both anandamide and non-selective CB1/CB2 receptors agonist HU-210 decreased the incidence of ventricular arrhythmias and reduced infarct size through the activation of the CB2 but not the CB1 receptors [67]. Also in mouse myocardial ischemia/reperfusion model, the protective effect of a CB1/CB2 receptors agonist WIN55212-2 was abolished by the selective CB2 antagonist AM630 and not affected by the selective CB1 antagonist AM251 [68]. In this study, cardioprotection was associated with a decreased *myeloperoxidase* activity and downregulation of *interleukin-1beta* and *CXC chemokine ligand 8* in the heart [68]. Likewise, pretreatment with the CB2 antagonist AM630 abolished the protective effects of remote preconditioning on infarct size and arrhythmias, whereas pretreatment with the CB1 antagonist AM251 had no significant effect on ischemia-induced arrhythmias or the infarct size [69].

Direct CB2 receptor activation by selective agonist JWH-133 during heart ischemia also reduced the infarct size [70] and prevented apoptosis through inhibition of the intrinsic mitochondria-mediated apoptotic pathway and involvement of the *PI3K/Akt* signal pathway [71].

Recently, Waldman et al. [72] observed a specific effect of non-selective activation of CB1/CB2 receptors by Δ -9-THC on ischemia/reperfusion in mice. Administrated in a very low dose (0.002 mg/kg), which is 3–4 orders of magnitude lower than the conventional doses, Δ -9-THC reduced infarct size and accumulation of neutrophils in the heart. This study also provided evidence for a wide therapeutic time window (2–48 h before ischemia) using extremely low dose of the cannabinoid drug.

Summarizing, during early and delayed ischemic preconditioning, cannabinoids activate long-lasting protective mechanisms in the heart predominantly via the CB2 receptors. The cellular mechanisms, by which endocannabinoids have a protective function by ischemia/reperfusion, include anti-apoptosis [71], prevention of inflammation [68, 72], induction of the heat shock protein 72 as well as prevention of calcium overload, and oxidative stress (reviewed in [13]).

6. Myocardial infarction and left ventricular remodeling

Acute phase post-myocardial infarction is characterized by cell death and inflammatory response, whereas in the late phase post infarction, collagen deposition, interstitial fibrosis, and extracellular matrix degradation contribute to cardiac remodeling processes [73]. Pathological left ventricular remodeling leads to progressive left ventricular dilatation and dysfunction, cardiac fibrosis, and the development of heart failure. Recent data provide evidence that cannabinoids might modulate many of these pathological processes, although the direct role of receptor subtype and interaction mechanisms is not clearly defined.

Administration of CB1 selective antagonist AM251 for 12 weeks promoted **left ventricular remodeling** indicated by left ventricular volume in rats with large myocardial infarction, whereas the nonselective cannabinoid agonist HU-210 enhanced left ventricular performance [16]. Hence, in this study, the CB1 blockade had negative effects on cardiac function post myocardial infarction, although this observation was significant only in rats with large myocardial infarction.

On the other hand, recent studies suggest that the blockade of the CB1 receptor may be protective. For example, chronic treatment with the CB1 receptor antagonist rimonabant reduced infarct size in wild-type mice but not in CB1^{-/-} mice in acute ischemia/reperfusion injury. Importantly, the protective effects were independent from weight reduction and adiponectin levels [74].

Our group described the protective effects of the CB1 receptor antagonist rimonabant on cardiac remodeling in a rat model of myocardial infarction and in metabolic syndrome [30]. Pretreatment with rimonabant prevented left ventricular dilatation and cardiac dysfunction in the early and late phase after myocardial infarction. This was evidenced by an improvement of functional cardiac parameters such as left ventricular internal diameter, ejection fraction, fractional shortening and dP/dt_{max} , dP/dt_{min} [30]. Moreover, rimonabant prevented electrocardiographic abnormalities and elevation of serum *brain natriuretic peptide* (BNP) levels, increased the cardiac protein expression of *SERCA2a* and improved pulse wave reflection. Importantly, preventive treatment was even more effective compared to post-ischaemic treatment regime. This finding is in agreement with the study performed by Lim et al. [74] where rimonabant administration 7 days—but not shortly—before ischemia reduced infarct size via a CB1-related mechanism. This fact confirms the importance of ECS in ischemic preconditioning.

Left ventricular remodeling post-myocardial infarction is also associated with **hypertrophy** in noninfarcted myocytes due to wall stress and activation of the local hormones. Antigrowth effect of anandamide was recently demonstrated in neonatal rat ventricular myocytes [75]. In this study, the ability of R-methanandamide to suppress myocyte enlargement and fetal gene activation was mediated by CB2 and CB1 receptors, respectively.

The late phase post-myocardial infarction is characterized by **cardiac fibrosis** associated with altered cardiac performance and arrhythmogenesis. Endocannabinoids may modulate either pro- or anti-fibrosis, depending on their interaction with CB1 or CB2 receptors, respectively [76, 77]. In the heart and aorta, CB1 antagonist rimonabant decreased collagen accumulation and prevented the upregulation of pro-fibrotic protein *TGF- β 1* in the remote myocardium after ischemia [30]. On the other hand, genetic deletion of CB2 receptors increased *TGF- β 1* and collagen production in the chronic heart failure model [52], indicating again that CB1 and CB2 receptors have opposing effects on fibrotic processes.

Furthermore, **extracellular matrix degradation** contributes to left ventricular wall-thinning in the remote region after myocardial infarction [78]. Since CB1 antagonist rimonabant dose-dependently reduced the activity of matrix metalloprotease MMP-9 in cardiac fibroblasts [30], CB1 receptors might be involved in proteolytic mechanisms. In addition, CB1/CB2 receptors are present in immune cells [23] through which they could modulate cytokine secretion and influence matrix remodeling.

Endothelial dysfunction and collagen accumulation contribute to increased pulse wave reflection and increase after load in patients with heart failure. It was initially suggested that inhibition of CB1 receptor deteriorates endothelial function after experimental myocardial infarction [16]. However, recent investigations showed that the inhibition of CB1 receptor is beneficial by endothelial dysfunction. It improved endothelium-dependent relaxation of aortic rings via a mechanism that involves downregulation of AT1 receptor expression [79] and ameliorated pulse wave reflection after experimental myocardial infarction in the rat [30].

As mentioned above in **heart failure**, ECS may become over-activated and contribute to depressed cardiac function, which can be attenuated by CB1 antagonists (reviewed in [14]). In doxorubicin-induced heart failure mouse model, pretreatment with CB1 antagonists improved doxorubicin-induced cardiac dysfunction by anti-inflammatory, antioxidative, and cytoprotective mechanisms [21]. Importantly, this and other studies suggested that beneficial effects of CB1 antagonists on contractile functions may extend beyond inhibition of CB1-mediated negative inotropic effect. Moreover, the protective role of CB1 inhibition may be partly explained by the activation of unopposed CB2 receptors because tissue endocannabinoids levels are elevated by cardiac diseases. The cellular CB2 receptor-mediated mechanisms, in turn, include increased *nitric oxide (NO)* production by induction of *NO synthase (iNOS)* [16], prevention of calcium overload through inhibition of I_{NCX} [45], prevention of *TNF- α* induced chemotaxis [70], and activation of anti-apoptotic [71], anti-inflammatory, and anti-atherogenic pathways (reviewed in [11]).

7. Conclusion

Endocannabinoids exert their actions in the heart mostly via the stimulation of the CB1 and the CB2 receptors. These receptors modulate pathophysiological processes following myocardial injury such as left ventricular remodeling, cardiac fibrosis, hypertrophy, and endothelial dysfunction.

Activation of cardiovascular CB1 receptors leads to depressed cardiac contractility and hypotension. Conversely, in most studies, the CB1 receptor antagonists are cardioprotective against ischemia–reperfusion injury, myocardial ischemia, heart failure, arrhythmias, and cardiomyopathies. The CB1 receptor antagonists also exert beneficial anti-apoptotic, anti-inflammatory, and anti-oxidative actions which are beyond inhibition of CB1-mediated negative inotropic effect.

Evidence to date indicates that CB2 receptor activation is cardioprotective. CB2 receptor-mediated effects such as anti-inflammation and anti-fibrosis may be in part opposite to the actions of the CB1 receptor. Given that tissue endocannabinoids levels are increased by cardiac injury, the protective role of CB1 inhibition may be partly explained by the activation of unopposed CB2 receptors. This fact requires further investigations. Moreover, little is known about the interaction of the CB1/CB2 receptors with other receptors like angiotensin-II receptors or PPARs as well as the role of new discovered putative endothelial cannabinoid receptor CBe and endocannabinoid metabolic products in cardiac diseases.

The endocannabinoid system indeed could represent a novel pharmacological target in treatment of cardiac disease. However, therapeutic use of cannabinoids, their synthetic analogs and cannabinoid receptor agonists/antagonists remain limited due to their psychotropic adverse effects. Therefore, it is necessary to develop newer compounds without actions on central nervous system.

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