Review Article

Cannabinoids for Treating Cardiovascular Disorders: Putting Together a Complex Puzzle

Basma Ghazi Eid

Department of Pharmacology and Toxicology, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia

Abstract

Cannabinoids have been increasingly gaining attention for their therapeutic potential in treating various cardiovascular disorders. These disorders include myocardial infarction, hypertension, atherosclerosis, arrhythmias, and metabolic disorders. The aim of this review is to cover the main actions of cannabinoids on the cardiovascular system by examining the most recent advances in this field and major literature reviews. It is well recognized that the actions of cannabinoids are mediated by either cannabinoid 1 or cannabinoid 2 receptors (CB_2Rs). Endocannabinoids produce a triphasic response on blood pressure, while synthetic cannabinoids show a tissue-specific and species-specific response. Blocking cannabinoid 1 receptors have been shown to be effective against cardiometabolic disorders, although this should be done peripherally. Blocking CB_2Rs may be a useful way to treat atherosclerosis by affecting immune cells. The activation of CB_2Rs was reported to be useful in animal studies of myocardial infarction and cardiac arrhythmia. Although cannabinoids show promising effects in animal models, this does not always translate into human studies, and therefore, extensive clinical studies are needed to truly establish their utility in treating cardiovascular disease.

Keywords: Cannabinoid 1 receptor, cannabinoid 2 receptor, cannabinoids, cardiovascular, metabolic disorders

Introduction

Cannabinoid compounds are being extensively studied for their wide range of therapeutic potentials. Although there is an abundance of information on the role of cannabinoids in the central and peripheral nervous systems, their role in the cardiovascular system seems to be more complex. The aim of this review is to cover the role that cannabinoids play in the treatment or prevention of various cardiovascular diseases including blood pressure, metabolic disorders, atherosclerosis, myocardial infarction, and cardiac arrhythmia. In addition, the most recent advances in this field and the challenges and negative effects of cannabinoids on human participants will be highlighted.

History of Cannabinoids and Their Mechanism of Action

Cannabinoids have traditionally been known for acting on the central nervous system. tetrahydrocannabinol (THC), which was first extracted from Cannabis sativa by Gaoni and Mechoulam in 1964, has been extensively studied and shown to have psychoactive properties.[1] Since then, it has been shown that cannabis contains over 80 active constituents.[2] In addition to naturally occurring cannabinoids, several endogenous cannabinoid compounds (endocannabinoids), such as N-arachidonoyl ethanolamine (AEA)[3] and 2-arachidonoyl glycerol (2-AG),[4,5] have been identified and examined. AEA is inactivated *in vivo* by fatty acid amidohydrolase[6] whereas 2-AG is inactivated by monoglyceride lipase with other enzymes playing a more minor role in their inactivation.[7] Cannabinoid receptors consist of two main forms, namely cannabinoid 1 receptor (CB_1R) and cannabinoid 2 receptor (CB_2R). They are both classified as G-protein-coupled receptors.[8] CB_1R is present in the central nervous system as well as other peripheral sites such as the cardiovascular, respiratory, reproductive, and digestive systems.[9] CB_2R is a peripheral receptor found in immune cells and organs.[10] The behavioral properties of cannabinoids have been shown to be

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Address for correspondence: Dr. Basma Ghazi Eid, Department of Pharmacology and Toxicology, Faculty of Pharmacy, King Abdulaziz University, PO Box 80260, Jeddah 21589, Kingdom of Saudi Arabia.
E-mail: beid@kau.edu.sa

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mediated by CB_1R[8,11,12] whereas CB_2R is mainly implicated in immunomodulation.[13]

Several studies have explored targeting the endocannabinoid system to treat various vascular diseases and disorders such as myocardial[14] and cerebral ischemia, hypertension[15] circulatory shock,[16] atherosclerosis, metabolic syndrome, stroke,[17] arrhythmia, and myocardial infarction.[18] Furthermore, studies have reported positive as well as negative effects of cannabinoids when used to combat cardiac disorders[19] and there seems to be a complicated relationship between the endocannabinoid system, the cardiovascular, and the immune system.

Effects of Cannabinoids on the Heart, Blood Pressure, and Vasculature

It is well known that acute exposure to cannabis leads to tachycardia, although the effect on blood pressure is less consistent.[20-22] On the contrary, chronic exposure was reported to cause bradycardia and a lowering of blood pressure.[15,23] The endocannabinoids AEA and 2-AG are present in various parts of the vasculature including red blood cells, platelets, serum and vascular cells, and the myocardium.[24-26] The activation of CB_1R in the myocardial tissue produces a negative inotropic response on the heart.[17,27-29] Although the expression of CB_2R has been demonstrated in cardiac myocytes[30,31] and in endothelial and smooth muscle cells of coronary arteries,[32,33] their role has been less well characterized and requires further investigation.[15]

The effects of endocannabinoids on blood pressure are not different from those of cannabis. The intravenous administration of AEA and 2-AG has been reported to cause a triphasic response that ultimately causes a lowering of blood pressure in experimental animals.[34] Although it was postulated in the 1970s that modulation of cannabinoid receptors could lead to the development of blood pressure-lowering agents, this was complicated by an overlap in the cardiovascular and neurological effects.[15] In recent years, however, it was shown that cannabinoids have a more profound blood pressure-lowering effect on hypertensive animals when compared to their nondiseased counterparts.[17,28,35-37] This has led to the rebirth of the hypothesis that cannabinoid ligands may indeed be used to target hypertension. The vasodilatory response of endocannabinoids has been shown to be partially attributed to the blockage of norepinephrine release from perivascular nerves in the sympathetic nervous system,[38] and partially, due to their ability to directly affect endothelial and vascular smooth muscle.[39]

When the effects of synthetic and endocannabinoids were studied on isolated blood vessels, there seemed to be a complex range of responses which proved to be species and tissue dependent.[17] In addition to the CB_1R, the involvement in a variety of other receptors, including the transient receptor potential vanilloid 1 receptor (TRPV1), has been shown to mediate the vascular effects of cannabinoids.[23,40,41] The activation of perivascular TRPV1 receptors by AEA in animal studies causes a cascade of events, whereby calcitonin gene-related peptide and various neuropeptides are produced ultimately activating vascular potassium channels and producing a dilatory response.[25,42,43] The vasodilatory effect of 2-AG has also been linked to the activation of TRPV4 in the endothelium and which ultimately activates calcium-dependent potassium channels in vascular smooth muscle cells.[44] The endocannabinoids, AEA, and 2-AG were shown to activate peroxisome proliferator-activated receptors (PPAR).[45] These may be exploited when using cannabinoids in treating cardiometabolic conditions since PPAR have widespread use in conditions displaying inflammation and tissue fibrosis.[46] Therefore, the actions of cannabinoids on vascular tone are complex and are mediated by a vast number of receptors which activate a wide range of signaling pathways.[22]

Cannabinoids may also affect local blood flow since they possess autocrine functions.[47] Studies have shown that endocannabinoid release in isolated arteries increases after exposure to vasoconstrictors such as angiotensin II.[24,48,49] To further support this activity, the presence of enzymes that metabolize cannabinoids in the vasculature has also been shown in a number of studies.[24,25] It has been demonstrated that endocannabinoids are released in ample amounts by white blood cells and platelets in certain inflammatory diseases.[26,28,50] These endocannabinoids subsequently exert their actions on the heart and vascular cells leading to vasodilation, lowering of blood pressure, and negative inotropy. Furthermore, various studies suggest that endocannabinoids may even mediate tissue remodeling in certain diseases.[51-53]

Cannabinoids in the Treatment of Metabolic Syndrome and its Associated Cardiac Complications

The role of the endocannabinoid system in metabolic syndrome has been an area of growing research interest over the past several decades. Furthermore, several animal models and clinical human trials have explored the therapeutic potential of CB_1R antagonists, such as rimonabant, for the treatment of metabolic diseases.[15] The expression of the CB_1R has been demonstrated in adipose tissue, whereby its activation is believed to cause an augmentation in lipolysis and an attenuation of oxidation of fatty acids.[54] CB_1R is also expressed in the liver where it is block counteracts fats and stenosis.[55] There have been reports of improved insulin resistance and glucose tolerance after CB_1R blockage in diet-induced and genetic animal obesity studies.[56]

Another beneficial effect of CB_1R blockage is the reversal of reduced heart contractility seen in many patients with cardiac diseases.[30,31] The patients suffering from obesity tend to have reduced heart contractility,[57,58] although this is frequently counteracted by excessive sympathetic stimulation

in these patients with a net result of a slight elevation of blood pressure, as is commonly seen in metabolic disorders where norepinephrine levels are reported to increase more than two-fold.[59] Rimonabant administration does not cause any change in blood pressure which further supports the idea of opposing mechanisms of action. Although cannabinoid antagonists may have beneficial effects, their use has been largely limited by their neuropsychiatric adverse effects such as depression and anxiety disorders.[60-63] Therefore, it is imperative that peripheral CB_1R antagonists are developed which possess the beneficial effects, yet lack the unwanted adverse effects.

Cannabinoids for the Treatment of Atherosclerosis

It is still unclear whether cannabinoids can be truly useful for the treatment of atherosclerosis. Although endocannabinoids may have beneficial effects in certain cardiovascular disorders, they actually possess a prothrombic effect.[64] Studies in humans and rats have reported platelet activation by anandamide and 2-AG. Platelets have a well-recognized role in maintaining blood homeostasis and in the formation of thrombi. Furthermore, the platelets possess anti-inflammatory actions and regulate growth. These properties may collectively contribute to the development of atherosclerosis.[65] Endocannabinoids may also be produced by platelets, macrophages, and endothelial cells, when an atherosclerotic plaque is formed. The increased level of endocannabinoids is counteracted by the metabolic properties of platelets, macrophages, and endothelial cells.[64]

CB_2R receptors have been proposed to play a role in the development of atherosclerosis. A study in an experimental model of atherosclerosis showed that THC in low doses was beneficial for treating atherosclerotic plaques.[66] The same study showed that the CB_2R receptor blocker SR144528 reversed this effect. Both synthetic and endogenous cannabinoids are involved in the mobilization of immune cells by CB_2R activation.[60]

The Role of Endocannabinoids in Myocardial Infarction

Several studies point to the important beneficial effects of endocannabinoids in protecting against myocardial infarction. One of the earliest studies testing this phenomenon looked at the effects on endocannabinoids on ischemic-isolated hearts with induced shock.[67] In that study, the cardioprotection was abolished after administering the CB_2R antagonist SR144528. Blocking CB_1R had no effect on the cardioprotection.[67] Other studies have reported that endocannabinoids lead to decreased necrosis of the myocardial tissue as well as lowering the risk of arrhythmia in acute myocardial infarction, and they are also involved in remodeling in the chronic stage.[68,69] The protective effect of endocannabinoids may be attributed to an action on endothelial cells as well as other mechanisms involving CB_1R and CB_2R.[70,31] CB_2R has been shown to play a key protective role when activated.[9] This has been linked to an attenuation of the inflammatory response and endothelial activation. Studies on knock-out mice also confirm the important role of CB_2R activation in protecting against myocardial infarction.[9,71]

Intravenous AEA injection was shown to upregulate heat-shock protein 72 in cardiac tissues. This provided cardiac protection against ischemia/reperfusion injuries in rodents. This effect was unaffected by the administration of a CB_1R blocker, but abolished after CB_2R blockade further supporting the important role of CB_2R in myocardial infarction.[72] Other studies looked at the benefits of CB_2R agonists in mice suffering from myocardial infarction using a model of ischemia/reperfusion and showed that mitogen-activated protein kinase as well as protein kinase C maybe involved in the CB_2R-mediated protection.[73,74] The effects on leukocyte migration are thought to underlie the cardioprotective effects of cannabinoids, as demonstrated in a study by Di Filippo *et al*.[75] They showed that the activation of CB_2R reduced the myocardial infarction size by half and caused a decline in leukocyte migration. This effect was reversed when a cannabinoid antagonist was administered further supporting their findings.[75]

Cannabinoids for Treating Cardiac Arrhythmia

Since most of the patients that suffer from a myocardial infarction tend to develop arrhythmia as a complication, it is also important to explore the role that the cannabinoid system plays in controlling this detrimental complication. Endocannabinoids have been shown to decrease the risk of developing cardiac arrhythmia, an effect which is mediated mainly by CB_2R.[70,76-78] A study looking at the effects of AEA in an arrhythmia model induced by ischemia found that it led to a significant decrease in the arrhythmia events.[77] This effect of AEA disappeared if the CB_2R antagonist SR144528 was given, but not after administration of the CB_1R antagonist rimonabant.[78] The CB_2R agonist, HU-210, showed nearly a complete reversal of the arrhythmia observed in both an ischemia model and epinephrine-induced and aconitine-induced model.[79-81] All these studies highlighted the important role that CB_2R receptors play over CB_1R in the antiarrhythmia effects of cannabinoids.[9] Furthermore, a study of cannabidiol in rats with cardiac injury showed that it caused a significant reduction in the ischemia-induced arrhythmias[82] an effect which was later shown to be mediated by potassium channels.[83]

Negative Effects of Cannabinoids on the Cardiovascular System in Humans

Although several animal studies have provided a promising role for both endocannabinoids and synthetic cannabinoids in treating and preventing certain cardiovascular disorders, this unfortunately does not always translate well in human trials. In fact, a large body of research has shown that the signaling of CB_1R can have detrimental effects on the cardiovascular system. Drop in blood pressure,[84] tachycardia,[84] increased

heart rate[85] and higher incidence of a heart attack were all reported in otherwise healthy young cannabis users.[86] Furthermore, it has been demonstrated that the synthetic cannabinoid K2 may cause healthy young children to suffer from myocardial infarction.[87] Another study by Heath *et al*.[88] reported that adolescents suffered from an increase in heart rate, unconsciousness, and pain.

It is postulated that the mediation of CB_1R leads to unwanted cardiac effects whereas CB_2R has more protective and anti-inflammatory action.[9,89] Other than affecting the cardiovascular system, the endocannabinoid system was reported to play a key role in various body functions including the gastrointestinal tract.[90] Endocannabinoids have also been reported to mediate the activities of cyclooxygenase enzyme, which is activated in certain gastric inhibitory responses to THC as well as in the hindbrain to mediate the inhibitory cardiac effects.[91]

Conclusion

Cannabinoids are increasingly being recognized for their wide range of therapeutic effects both in the cardiovascular system and on other systems in the human body. Both endocannabinoids and synthetic cannabinoid compounds have been widely studied and proven to be useful in treating a large number of cardiac disorders. However, there still seems to be a dimension of complexity that accompanies these compounds which exert effects on CB_1R, CB_2R as well as other noncannabinoid receptors. Although several rodent models have shown promising actions of cannabinoids on the cardiovascular system, indeed we are a long way from seeing these compounds on the market. It is, therefore, required that the cannabinoid compounds with promising effects in animal studies be taken to the next stage and studied in humans. These clinical studies will shed light on the true therapeutic potential of cannabinoids in the cardiovascular system.

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Conflicts of interest

There are no conflicts of interest.

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