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Role of cannabinoids and the endocannabinoid system in modulation of diabetic cardiomyopathy

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Abstract

Diabetic complications, chiefly seen in long-term situations, are persistently deleterious to a large extent, requiring multi-factorial risk reduction strategies beyond glycemic control. Diabetic cardiomyopathy is one of the most common deleterious diabetic complications, being the leading cause of mortality among diabetic patients. The mechanisms of diabetic cardiomyopathy are multi-factorial, involving increased oxidative stress, accumulation of advanced glycation end products (AGEs), activation of various pro-inflammatory and cell death signaling pathways, and changes in the composition of extracellular matrix with enhanced cardiac fibrosis. The novel lipid signaling system, the endocannabinoid system, has been implicated in the pathogenesis of diabetes and its complications through its two main receptors: Cannabinoid receptor type 1 and cannabinoid receptor type 2, alongside other components. However, the role of the endocannabinoid system in diabetic cardiomyopathy has not been fully investigated. This review aims to elucidate the possible mechanisms through which cannabinoids and the endocannabinoid system could interact with the pathogenesis and the development of diabetic cardiomyopathy. These mechanisms include oxidative/nitrative stress, inflammation, accumulation of AGEs, cardiac remodeling, and autophagy. A better understanding of the role of cannabinoids and the endocannabinoid system in diabetic cardiomyopathy may provide novel strategies to manipulate such a serious diabetic complication.

Key Words: Δ 9-tetrahydrocannabinol; Autophagy; Cannabinoid receptors; Diabetic cardiomyopathy; Endocannabinoid system; Inflammation

Core Tip: Diabetic cardiomyopathy is considered to be one of the most common deleterious diabetic complications being the leading cause of mortality among diabetic patients. The endocannabinoid system has been implicated in the pathogenesis of diabetes and its complications. However, the role of the endocannabinoid system in diabetic cardiomyopathy has not been fully investigated. This review aims to elucidate the possible mechanisms through which cannabinoids and the endocannabinoid system could interact with the pathogenesis of diabetic cardiomyopathy. Better understanding of the role of cannabinoids and the endocannabinoid system in diabetic cardiomyopathy may provide novel strategies to manipulate this serious diabetic complication.

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INTRODUCTION

Diabetes mellitus is one of the most common chronic disorders worldwide, and it continues to increase in number and significance. The total number of individuals with diabetes worldwide is 463 million, with a prevalence rate of 9.3% according to the International Diabetes Federation[1]. It is estimated that the prevalence of diabetes on a global scale could reach 578 million by 2030 and 700 million by 2045. In 2017, diabetes-related mortality accounted for 4 million people worldwide and the total healthcare expenditure reached 727 billion United States Dollars[2].

Diabetes mellitus is a complex metabolic condition that is characterized by hyperglycemia resulting from a lack of absolute or relative insulin[3]. It is linked to insulin resistance in many instances. Type 1 diabetes is caused by an autoimmune destruction of insulin-secreting cells in the pancreas, and type 2 diabetes is caused by insufficient compensatory insulin production in the presence of peripheral insulin resistance. Ninety percent of diabetes cases are of the latter type[4].

Both microvascular (retinopathy, nephropathy, and neuropathy)[5-9] and macrovascular (cardiovascular disease) problems are linked to diabetes[6-10]. Despite substantial advances in anti-diabetic therapy, diabetic complications, which are most commonly recognized in the long-term, are consistently harmful to a large extent, necessitating multi-factorial risk reduction measures beyond glycemic control[11]. Diabetes-related morbidity and mortality are primarily caused by cardiovascular problems[12]. Indeed, 50% of diabetic patients die of a cardiovascular disease[13]. Endothelial dysfunction, coronary artery disease, and myocardial left ventricular dysfunction (which leads to heart failure) are all well-known cardiovascular problems[14]. Diabetic patients have a 2-4 times higher risk of heart failure than non-diabetic patients, according to clinical research[15,16].

Diabetic cardiomyopathy is a deficiency in ventricular contractile function that occurs in diabetic individuals regardless of the presence of coronary artery disease or other cardiovascular disorders. It is a complicated diabetes-related condition marked by severe alterations in the heart's physiology, anatomy, and mechanical performance[17]. Diabetic cardiomyopathy is a complicated and poorly understood process. To explain the structural and functional alterations associated with diabetic cardiomyopathy, several pathogenic processes have been explored and suggested[18]. Increased oxidative/nitrative stress[19-21], accumulation of advanced glycation end products (AGEs)[22], activation of various pro-inflammatory and cell death signaling pathways[23], and changes in the composition of extracellular matrix with elevated cardiac fibrosis[24] are some of the proposed pathological mechanisms. Unfortunately, despite the growing body of information concerning diabetic cardiomyopathy over the last few decades, therapeutic choices remain inadequate. Other treatments for diabetic cardiomyopathy's multi-factorial pathogenic pathways have yet to be developed.

The endocannabinoid system is an endogenous lipid signaling system that consists of: (1) Two main receptors identified as cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2); (2) Endogenous ligands for these two receptors known as endocannabinoids; and (3) Proteins that control endocannabinoid tissue levels (anabolic and catabolic enzymes)[25]. The endocannabinoid system has become a novel therapeutic target in a range of cardiovascular illnesses in the last decade, including atherosclerosis, myocardial infarction, and heart failure[26]. Furthermore, the significance of the endocannabinoid system in the development of diabetes and associated consequences has been suggested in various pre-clinical and clinical research[27-29]. The possible mechanisms through which cannabinoids and the endocannabinoid system could modulate the pathogenesis of diabetic cardiomyopathy are highlighted in this review (Table 1), an approach that could pave the way for the use of this

Table 1 Role of cannabinoid agents in diabetes

Cannabinoid agent	Mechanism	Role in diabetes
Anandamide	Endogenous cannabinoid CB1 agonist CB2 agonist	Elevated in diabetic patients[26]
Rimonabant (SR141716A)	CB1 antagonist	Reduced weight[62] Reduced hemoglobin A1c levels[62] Reduced fasting blood glucose levels[62] Reduced high density lipoprotein, cholesterol and triglyceride levels[62] Improved systolic blood pressure[62]
Δ 9-tetrahydrocannabinol (THC)	Psychoactive cannabinoid CB1 partial agonist CB2 partial agonist	Lowered blood glucose level[65]; Preserved pancreatic insulin content[65]
Cannabidiol	Non-psychoactive cannabinoid Low affinity to CB1 and CB2	Reduced the incidence of type I diabetes[66] Immunosuppressive effect[66]

system as an effective tool in the management of these harmful diabetic complications.

DIABETIC CARDIOMYOPATHY: A DISTINCT COMPLEX DISORDER

Cardiomyopathies are a group of diseases characterized by myocardial dysfunction that is not induced by common causes, such as coronary artery disease, valvular dysfunction, or hypertension. Cardiomyopathies are divided into four categories depending on hemodynamic characteristics: Dilated, hypertrophic, restrictive, and obliterative cardiomyopathy[30]. Dilated cardiomyopathy is characterized by ventricular dilatation and systolic dysfunction, which commonly affects both ventricles. The most common symptom of hypertrophic cardiomyopathy is significant ventricular hypertrophy. Restrictive cardiomyopathy is characterized by inflexible and poorly distensible myocardium, resulting in poor compliance. Endo-myocardial fibrosis is a symptom of obliterative cardiomyopathy. The endocardium's severe fibrosis encroaches on and reduces the size of the ventricular cavities[31]. Diabetic cardiomyopathy can be classified as either dilated or hypertrophied cardiomyopathy[32].

Rubler *et al*[33] coined the name diabetic cardiomyopathy in 1972 after observing a specific type of cardiomyopathy in diabetic patients who did not have other cardiovascular issues such as coronary artery disease, valvular or congenital heart disease, or hypertension. Diabetic cardiomyopathy is defined by a series of cardiac alterations, including interstitial fibrosis, myocardial hypertrophy, and microcirculatory abnormalities, that arise due to diabetes mellitus. These circulatory issues impair heart function, eventually leading to cardiac failure[4]. Heart failure lowers an individual's quality of life and makes diabetes control more difficult. As a result, early diagnosis and treatment of these patients are regarded as top priorities[34].

Insulin resistance and hyperglycemia are significant drivers in diabetic patients, activating a variety of adaptive and maladaptive responses that ultimately affect cardiac function[35]. To explain the complicated structural and functional abnormalities associated with diabetic cardiomyopathy, several pathogenic processes have been examined and proposed (Figure 1). These systems work in concert and may even enhance one another[36]. Hyperglycemia increases oxidative stress by accelerating glucose oxidation and mitochondrial production of reactive oxygen species (ROS), which induce DNA damage and promote apoptosis[37]. AGEs build up in tissues, including the myocardium, and have been linked to structural abnormalities in diabetic hearts[22]. Activation of numerous pro-inflammatory and stress signaling pathways, such as mitogen activated protein kinases (MAPKs), also stimulates apoptotic pathways and cell death, and promote myocardial cell death[23,38]. Finally, there is increased collagen formation in the myocardium that leads to fibrosis and reduced contractile function of the heart[24,39].

Diabetic cardiomyopathy is divided into three stages (Figure 2): Early-stage, middle-stage, and late-stage[4]. In the early stage, the heart develops hypertrophy and has diastolic dysfunction with normal ejection fraction, and it is asymptomatic[40]. Increased left ventricular size, wall thickness, and mass, as well as diastolic dysfunction and a modest decline in systolic performance, characterize the intermediate stage. Insulin resistance, AGE formation, elevated renin-angiotensin-aldosterone system levels, apoptosis, necrosis, and fibrosis are all associated with this stage[41]. As the disease progresses from the

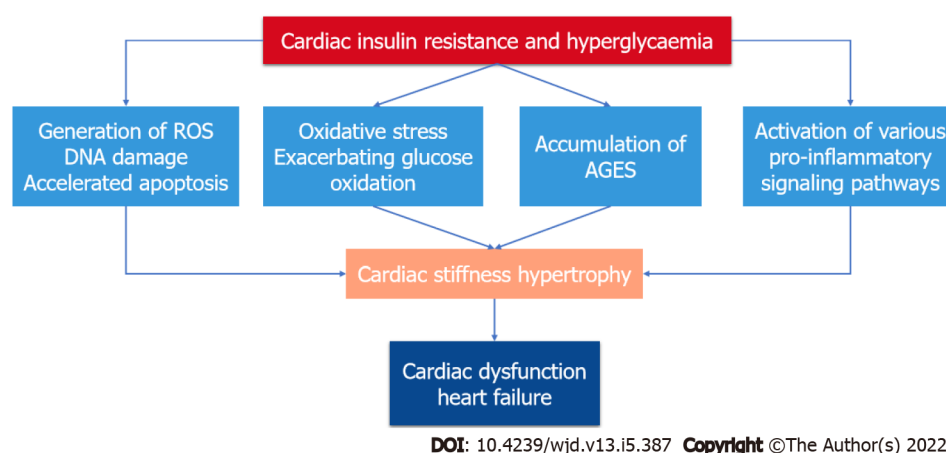


Figure 1 Molecular mechanisms of diabetic cardiomyopathy. Hyperglycemia and insulin resistance increase reactive oxygen species formation, oxidative stress, advanced glycation end-products formation, and the recruitment of various inflammatory pathways leading to cardiac dysfunction and heart failure. ROS: Reactive oxygen species.

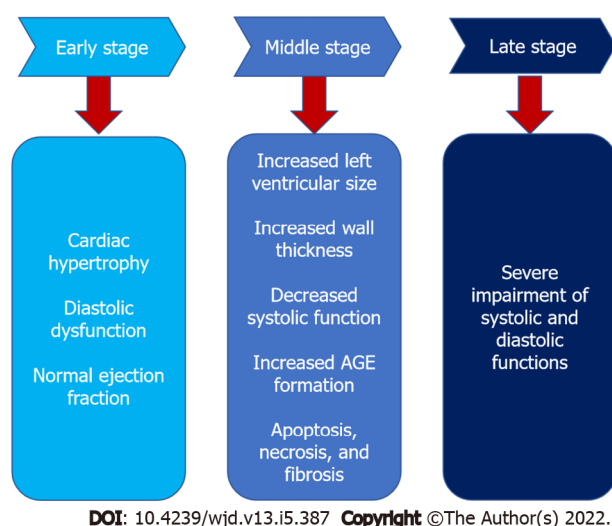


Figure 2 Stages of diabetic cardiomyopathy progression. Diabetic cardiomyopathy progresses from early development of hypertrophy and diastolic dysfunction that then progress to decreased systolic activity, apoptosis and cardiac fibrosis leading to severe impairment in both systolic and diastolic functions. AGE: Advanced glycation end products.

medium to late stage, it becomes more severe, impairing both systolic and diastolic functioning[13].

THE ENDOCANNABINOID SYSTEM

The discovery of the endogenous signaling system now recognized as the endocannabinoid system began with the chemical detection of 9-tetrahydrocannabinol (THC), the main psychoactive component of *Cannabis sativa*[42]. THC's psychotropic and immunomodulatory effects are due to the ability to bind to and activate specific receptors, including the CB1 receptor, which is one of the most abundant G-protein-coupled receptors in the central nervous system[43], and the CB2 receptor, which is abundantly expressed in several immune cells and tissues[44].

The existence of endogenous substances (the endocannabinoids) capable of binding to and activating CB1 and CB2 receptors was suggested. Anandamide (N-arachidonoyl ethanolamine)[45] and 2-arachidonoyl glycerol (2-AG)[46] are the two most well-studied examples of these compounds. The endocannabinoid system is made up of cannabinoid receptors, endocannabinoids, and proteins that catalyze endocannabinoid biosynthesis (N-acyl-phosphatidylethanolamine phospholipase-D for anandamide and diacylglycerol lipases for 2-AG), transport, and inactivation [fatty acid amide hydrolase (FAAH) for anandamide and monoacyl glycerol lipase for 2-AG][47]. Signaling *via* CB1 and CB2 receptors is complex, involving inhibition (and activation in some cases) of adenylyl cyclase activity,

activation of various MAPKs [*e.g.*, p38- and p44/42-MAPKs, c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK)], protein kinases A and C (PKA and PKC), and modulation of various calcium and potassium channels[48].

Since its discovery about two decades ago, the endocannabinoid system has gained considerable importance as a fundamental signaling system implicated in almost all physiological and pathological processes in animals[49]. In a wide range of pathological conditions, including mood and anxiety disorders, movement disorders, neuropathic pain, multiple sclerosis, cancer, glaucoma, osteoporosis, reproductive disorders, immune dysfunction, cardiovascular and metabolic disorders, there is growing evidence that the endocannabinoid system plays pivotal roles and holds tremendous therapeutic options[50,51].

Besides the primary distribution of CB1 receptors in the CNS and CB2 receptors in immune cells, as these are responsible for the psychoactive and immunomodulatory effects of cannabinoids, both receptors have been found to be expressed in cardiovascular system cells such as cardiomyocytes, fibroblasts, endothelial and vascular smooth muscle cells, and infiltrating immune cells[26]. CB1 receptors activation by endocannabinoids or synthetic ligands has complex depressive effects in the cardiovascular system and has been linked to the development of pathophysiological alterations and compromised cardiovascular function in various forms of shock[51] and heart failure[52]. In addition, several studies indicated that stimulation of CB1 receptors in the cells of the cardiovascular system is associated with activation of stress signaling pathways promoting cell death, ROS production, and induction of inflammatory cascades[26,52]. On the other hand, an increased CB2 receptor expression has been reported in the cardiovascular system under pathophysiological conditions such as inflammatory stimulation or tissue injury, which likely reflects a protective response to limit these effects[53]. A great body of evidence suggest a protective role of CB2 receptors in experimental models of cardiovascular disorders including mouse models of atherosclerosis[54], restenosis[55] and myocardial ischemia/reperfusion injury[56].

Different expression patterns of CB1 and CB2 receptors together with other components of the endocannabinoid system such as synthesizing and degrading enzymes have been reported in islet cells of humans, rats and mice[57-59]. There are controversial results regarding the role of CB1 receptors in insulin secretion with studies showing an increased insulin secretion in islet cells by activation of CB1 receptors[57,58], and others showing decreased insulin secretion[60]. In addition, activation of CB2 receptors in islet cells has also been shown to either stimulate[61] or attenuate insulin secretion[57]. Several studies have found that the endocannabinoid system plays a significant role in the etiology of diabetes. Serum levels of anandamide and 2-AG have been found to be greater in type 2 diabetics than in healthy individuals[27]. Furthermore, in these diabetic patients, subcutaneous tissue levels of anandamide were found to be elevated, indicating endocannabinoid system overactivity[28].

A clinical trial was conducted in obese patients with type 2 diabetes inadequately controlled by either metformin or sulfonylureas using the CB1 antagonist rimonabant (SR141716A). Rimonabant treatment caused a reduction in weight, hemoglobin A1c levels, fasting blood glucose, high-density lipoprotein cholesterol and triglycerides, as well as improvement in systolic blood pressure[62]. In the type 2 diabetic patients naive to anti-diabetic treatment, rimonabant showed similar results with improved glycemic control and metabolic profile[63]. Another study demonstrated that the treatment of type 2 diabetic patients on standard insulin treatment with rimonabant also improved glycemic control and the metabolic profile[64]. The psychoactive cannabinoid THC was shown to attenuate the severity of autoimmune responses in an experimental model of autoimmune diabetes in addition to lowering blood glucose level and preserving pancreatic insulin content[65]. Unfortunately, the psychoactive effects of THC hampered this therapeutic approach. The non-psychoactive cannabidiol (CBD) reduced the incidence of diabetes in a mouse model of type 1 diabetes, an effect that involved immunosuppressive and anti-inflammatory effects[66].

The majority of diabetic complications are linked to abnormalities in the vascular system[67]. Hyperglycemia has been related to a number of critical processes, including oxidative/nitrative damage, AGE buildup, and inflammatory system stimulation[68]. Endothelial dysfunction occurs in arteries, which contributes to the development of numerous diabetes problems. Indeed, cannabinoids and the endocannabinoid system represent an outstanding therapeutic approach to manage these deleterious complications. Interestingly, this notion is supported by a great body of evidence implicating the endocannabinoid system in the pathogenesis of nearly all diabetic complications including nephropathy, retinopathy, and neuropathy, in addition to cardiovascular complications, mainly through modulation of the aforementioned mechanisms[29]. Still, the role of the endocannabinoid system in diabetic cardiomyopathy; the distinct diabetic complication, has not been fully investigated in detail.

POSSIBLE MECHANISMS THROUGH WHICH CANNABINOIDS AND THE ENDOCANNABINOID SYSTEM COULD MODULATE DIABETIC CARDIOMYOPATHY

Oxidative/Nitrative stress

Nearly 95% of oxygen consumed by tissues is used in metabolic processes to produce adenosine triphosphate (ATP), and approximately 5% of oxygen consumed is transformed into superoxide ($O_2^{\cdot-}$) radical, the principal oxygen free radical produced by mitochondria[69]. The antioxidant enzymes superoxide dismutase (SOD1, SOD2, and SOD3) quickly convert superoxide to hydrogen peroxide (H_2O_2) within the cell[70]. Antioxidant enzymes such as catalase, glutathione peroxidase, and other peroxidases generally convert excess H_2O_2 to harmless water[71]. Although H_2O_2 is not a free radical, it can undergo the Fenton reaction with reduced transition metals [*e.g.*, ferrous ion (Fe^{2+})] or with superoxide in the presence of metal ions (usually iron or copper) to produce the highly reactive hydroxyl radical (OH), which is a far more damaging molecule to the cell[72]. Superoxide radicals can quickly react with nitric oxide (NO) to produce cytotoxic peroxynitrite anions ($ONOO^-$) in addition to producing H_2O_2 [73]. Superoxide and NO are less reactive than peroxynitrite, which might combine with carbon dioxide to generate nitrotyrosine, that triggers protein degradation and lipid oxidation[74].

Besides mitochondria, other cellular sources of reactive oxygen and nitrogen species (RNS) exist. NADPH oxidase, for example, promotes the enzymatic conversion of oxygen to superoxide anion. Several critical cytosolic proteins (p44phox, p67phox, p40phox, and Rac2) must be translocated to the cellular membrane for NADPH oxidase activation[75]. Other sources of ROS and RNS, in addition to NADPH oxidase, include nitric oxide synthase (NOS), which stimulates NO synthesis[76], and peroxisomes, that are known to create H_2O_2 primarily through fatty acid oxidation[77] and phagocytic cell activation[78].

The oxidative stress pathway has emerged as a common thread connecting all major diabetic cardiomyopathy pathophysiological mechanisms[79]. These pathways are the result of a single hyperglycemia-induced process: The overproduction of superoxide by the mitochondrial electron transport chain[80]. Formation of AGE products, auto-oxidation of glucose, activation of PKC, and NADPH oxidase are some of the other sources of ROS in diabetes[81]. Once oxidative stress develops, it results in a vicious self-sustaining cycle of generating more free radicals and causing more stress as a result of the activation of multiple stress-induced pathways and due to its ability to cause damaging effects to multiple components within the cell[82].

Through a variety of mechanisms, ROS induce cellular damage in the diabetic myocardium. Increased ROS directly damage cellular proteins and DNA[83]. In addition, ROS activate matrix metalloproteinases, which modify the extracellular matrix architecture and cause fibrosis[84], as well as regulating signal transduction pathways that cause cardiomyocyte hypertrophy[85] and apoptosis, which results in the loss of contractile tissue[86]. In a similar manner, peroxynitrite induces vasoconstriction, enhanced leukocyte adherence, platelet activation, oxidation, pro-thrombotic state, impaired coagulation, and vascular inflammation, among other pro-atherosclerotic pathogenic processes[87]. In type 1 diabetic mice, selective suppression of mitochondrial ROS was demonstrated to prevent diabetic cardiac abnormalities, confirming the importance of mitochondrial ROS role in developing cardiac abnormalities[88]. Moreover, Rac1 increases mitochondrial ROS generation *via* NADPH oxidase activation and plays an important role in cardiomyocyte death and cardiac failure in streptozotocin-induced diabetes in mice[89].

Previous studies have shown that the endocannabinoid system can influence ROS and RNS production, implying that modulating the endocannabinoid system and administering exogenous cannabinoids with antioxidant properties could be beneficial in the treatment of diabetes-related cardiovascular complications, such as diabetic cardiomyopathy[29].

It has been shown that genetic deletion of CB1 receptors attenuated the rise in markers of oxidative [4-hydroxy-trans-2-nonenal (4-HNE)] and nitrative (nitrotyrosine) stress in the myocardium of mice treated with acute or chronic doses of the potent, cardio-toxicant, anticancer drug doxorubicin[90]. In addition, doxorubicin treatment led to decreased myocardial content of the components of the antioxidant defense system: Glutathione, glutathione peroxidase, and SOD. These changes were significantly reduced in the myocardium of CB1 knockout mice[90]. Consistent with the data obtained from rodents, activation of CB1 receptors by anandamide or the potent agonist HU210, with or without doxorubicin, induced ROS production in human primary cardiomyocytes (HCM). The previous deleterious effect was attenuated by the use of CB1 antagonists: SR141716A or AM281[90].

Mukhopadhyay *et al*[52] similarly found that pharmacological blockage of CB1 receptors with AM281 or SR141716A reduced doxorubicin-induced oxidative/nitrative stress and related cell death. In comparison to their wild-type counterparts, mice lacking the FAAH gene showed a significant increase in acute and chronic doxorubicin-induced cardiac oxidative and nitrative stress, as well as impaired antioxidant defense and tissue injury[91]. Furthermore, anandamide increased the sensitivity of inflammatory cells isolated from FAAH mutant mice to ROS generation. These findings imply that, in pathological situations involving oxidative/nitrative stress (such as doxorubicin-induced myocardial injury), FAAH plays an important role in regulating endocannabinoid-induced cardiac cell injury, which is mediated in part by CB1 receptor activation because these effects may be attenuated by

selective CB1 antagonists[91].

The role of the endocannabinoid system in oxidative stress control has also been proven in atherosclerosis models such as the apolipoprotein E (ApoE) deficient animal model. In ApoE and CB2 double knockout mice, the release of superoxide radical was increased two-fold in intact aortic segments compared to ApoE knockout mice. The selective CB2 agonist JWH-133 reduced ROS release in ApoE knockout mice to comparable levels to those in wild-type animals[54].

The first evidence of a direct link between the endocannabinoid system and the pathogenesis of diabetic cardiomyopathy came from the interesting study conducted by Rajesh and co-workers in 2011. This research group demonstrated an increased expression of CB1 receptors and anandamide levels in the myocardium of streptozotocin-induced diabetic mice compared to their non-diabetic counterparts [92]. Streptozotocin-induced diabetic cardiomyopathy was characterized by a profound accumulation of markers of oxidative and nitrative stress in the myocardium, an effect that was ameliorated by genetic deletion of CB1 receptors. In addition, genetic deletion of CB1 mitigated the expression of the p40^{phox} NADPH oxidase active subunit in myocardial tissue of diabetic mice[92].

Earlier, the same research group demonstrated a protective effect of CBD in diabetic cardiomyopathy [92]. CBD is the most common non-psychotropic cannabinoid in *Cannabis sativa*, and it has been approved for the treatment of inflammation, pain, and spasms associated with multiple sclerosis in humans[93]. CBD exerts several actions that are independent of the CB1 and CB2 receptors[94]. In this study, CBD therapy was found to reduce oxidative and nitrative stress in the myocardium of streptozotocin-induced diabetic mice. Additionally, CBD was found to reduce ROS production as well as the expression of active ROS-generating NADPH oxidase isoforms p22^{phox}, p67^{phox}, and gp91^{phox}. It also increased glutathione levels and SOD activity and reduced nitrotyrosine production. These protective effects of CBD against oxidative/nitrative stress were also demonstrated *in vitro* in human primary cardiomyocytes[95].

In a study published in 2017, Vella *et al*[96] found that giving cannabinoids to diabetic rats reversed changes in lipid peroxidation and oxidative stress markers, as well as blocking maladaptive alterations in the structure and function of the heart and blood vessels. Similar findings were previously published by Rajesh's group, who reported that administering CBD to diabetic C57BL/6J mice for 11 wk reduced the formation of lipid peroxides, protein carbonyls, and ROS in the heart[95]. Furthermore, the binding site of anandamide has been linked to NO release[97], implying a possible mechanism by which cannabinoids could increase NO bioavailability. THC treatment of STZ-induced diabetic rats resulted in a controlled redox state that granted improvements in end organ function of the myocardium and vasculature[96]. This was demonstrated by preservation of myocardial pump function, cardiac electrophysiology, noradrenergic-mediated contraction, and endothelial-dependent relaxation of resistance arteries. These findings suggested that cannabinoid receptor activation in an experimental type I diabetes animal might be a potential pharmacological target for diabetic cardiomyopathy management [96] (Table 2).

Inflammation

Inflammation is a complex nonspecific response of vascular tissues to harmful stimuli such as pathogens, damaged cells, or irritants, and it involves several functional and molecular mediators, such as the recruitment and activation of leukocytes such as mast cells, neutrophils, and monocytes/macrophages. On an acute basis, inflammation is usually good since it represents the organism's defensive attempt to eliminate damaging stimuli and begin the healing process. Inflammation, on the other hand, might have negative consequences if it continues for a long period[98]. The increased expression of many inflammatory proteins is regulated at the level of gene transcription through the activation of pro-inflammatory transcription factors which play a critical role in amplifying and perpetuating the inflammatory process[99].

Activation of the transcription factor nuclear factor-kappa B (NF-κB), which binds to DNA and activates gene transcription, appears to play a pivotal role in the regulation of inducible enzymes such as inducible nitric oxide synthase (iNOS), inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6, prostaglandins, cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), in addition to other substances that are initiators or enhancers of the inflammatory process[100,101]. The aforementioned inflammatory mediators bind to specific target receptors on the cells and may increase vascular permeability, promote inflammatory cell chemotaxis, stimulate smooth muscle contraction, increase direct enzymatic activity, induce pain, and/or mediate oxidative damage[102].

Numerous investigations have indicated that inflammatory processes play a critical role in the development of diabetes macro- and microvascular complications[29,103]. Cardiac inflammation is a common and early symptom of diabetes, and it plays a key role in the progression of heart failure in diabetic cardiomyopathy[104]. Furthermore, various research on the heart of diabetic or diabetic hypertensive rats has shown that NF-κB plays a major role in the development of diabetic cardiomyopathy[105,106].

Cannabinoid receptor expression in immune cells can be influenced by various inflammatory factors and other triggers activating these cells[107]. Inflammatory stimuli may potentially boost the synthesis of endocannabinoids in immune cells (*e.g.*, macrophages, monocytes, and dendritic cells) by activating

Table 2 Summary of possible mechanisms by which cannabinoids and the endocannabinoid system could modulate diabetic cardiomyopathy

Cannabinoid agent	Mechanism	Effect
Endocannabinoids	Oxidative/Nitrative stress	Influenced ROS and RNS production[28]
	Myocardial remodeling	Triggered activation of signaling pathways (e.g., p38 and JNK-MAPKs), promoting cell death[50,137]
	Inflammation	Increased during inflammation[107] Modulating T and B lymphocyte proliferation and apoptosis, inflammatory cytokine production and immune cell activation by inflammatory stimuli[107,108,111]
AM281	Oxidative/Nitrative stress	Attenuated doxorubicin-induced oxidative stress[52]
SR141716A	Oxidative/Nitrative stress	Attenuated doxorubicin-induced oxidative stress[52]
	Inflammation	Reduced plasma levels of the pro-inflammatory cytokines MCP-1 and IL-12 in low density lipoprotein deficient mice[113] Inhibited LPS-induced pro-inflammatory IL-6 and TNF- α expression[113]
	Myocardial remodeling	Reduced activation of p38 and JNK/MAPK[90] Improved myocardial dysfunction induced in a mouse model of diabetic cardiomyopathy[92] Reduced markers of cell death (activated caspase-3 and chromatin fragmentation)[92]
JWH133	Oxidative/Nitrative stress	Reduced ROS release in ApoE knockout mice[54]
	Inflammation	Decreased leukocyte recruitment in ApoE-knockout mice[54] Attenuated TNF- α -induced NF- κ B activation[116] Attenuated ICAM-1 and VCAM-1 up-regulation[116]
Cannabidiol	Oxidative/Nitrative stress	Attenuated oxidative and nitrative stress in the myocardium of streptozotocin-induced diabetic mice[93] Prevented changes in markers of lipid peroxidation and oxidative stress in diabetic rats[96]
	Inflammation	Inhibited I κ B- α phosphorylation and subsequent p65 NF- κ B nuclear translocation[93] Attenuated high glucose-induced NF- κ B activation in primary human cardiomyocytes[93]
	Myocardial remodeling	Attenuated the established systolic and diastolic dysfunction in diabetic mice[93] Attenuated the activation of stress signaling pathways: p38 and JNK/MAPKs[93] Enhanced the activity of the pro-survival AKT pathway in diabetic myocardium[93] Decreased the activity of the pro-apoptotic enzyme caspase-3[93]
	Autophagy	Promoted endothelial cell survival <i>via</i> HO-1 mediated autophagy[170]
Anandamide	Oxidative/Nitrative stress	Induced NO bioavailability[97]
	Myocardial remodeling	Decrease rat heart mitochondrial O ₂ consumption[135] Increased activation of p38 and JNK/MAPK, followed by cell death[90] Enhanced doxorubicin-induced MAPK activation and cell death[90]
Δ 9-tetrahydrocannabinol (THC)	Oxidative/Nitrative stress	Regulated redox state in diabetic rats[96]
	Myocardial remodeling	Decreased rat heart mitochondrial O ₂ consumption[135]
WIN55, 212-2	Inflammation	Reduced atherosclerotic lesion macrophage content and IL-6 and TNF- α levels[114,115] Reduced adhesion molecules VCAM-1 and ICAM-1 as well as NF- κ B activation[114,115]

HU-308	Inflammation	Attenuated TNF- α -induced NF- κ B activation, ICAM-1 and VCAM-1 up-regulation[116] Decreased endothelial cell activation and suppression of the acute inflammatory response[56,117]
	Autophagy	Enhanced autophagy levels in heart tissues with diabetic cardiomyopathy [171] Increased AMPK phosphorylation while decreasing the phosphorylation of mTOR[171]
HU-210	Myocardial remodeling	Decrease rat heart mitochondrial O ₂ consumption[135] Increased activation of p38 and JNK/MAPK, followed by cell death[90] Enhanced doxorubicin-induced MAPK activation and cell death[90] Enhanced left ventricular performance in rats with myocardial infarction [143]
		Improved cardiac function in carbon tetrachloride-induced cirrhosis in rats[140]
		Reduced activation of p38 and JNK/MAPK[90]
AM251	Myocardial remodeling	

LPS: Lipopolysaccharide; AMPK: Adenosine monophosphate activated protein kinase; mTOR: Mammalian target of rapamycin; IL: Interleukin; JNK: Jun N-terminal kinase; MAPK: Mitogen activated protein kinases; TNF- α : Tumor necrosis factor- α ; NF- κ B: Nuclear factor-kappa B; ICAM-1: Intercellular adhesion molecule-1; VCAM-1: Vascular cell adhesion molecule-1.

multiple biosynthetic pathways and/or decreasing the expression of metabolic enzymes that degrade them[107,108]. THC and other natural or synthetic cannabinoids have been studied for their immunomodulatory effects in mice and/or rats *in vivo*, as well as in cultured human immune cells. Overall, cannabinoid ligands exhibit suppressive effects on B-lymphocytes, T-lymphocytes, natural killer cells, and macrophages[109,110], which are most likely due to both CB1 and CB2 receptor-dependent and -independent mechanisms. Other studies have revealed that endocannabinoids can influence immune functions by modulating T and B lymphocyte proliferation and apoptosis, inflammatory cytokine production and immune cells activation in response to inflammatory stimuli, macrophage-mediated killing of sensitized cells, chemotaxis, and inflammatory cell migration[107,110,111]. Furthermore, cannabinoids may influence the expression of iNOS and the formation of ROS in immune cells, which play significant roles in the defense against invading pathogens and in modulation of the inflammatory response[21]. The involvement of cannabinoid receptors in inflammation is shown in Figure 3.

Han *et al*[112] demonstrated that CB1 receptors promote pro-inflammatory responses of macrophages through ROS production, and subsequent synthesis of TNF- α and monocyte chemoattractant protein-1 (MCP-1). This effect was negatively regulated by CB2 and was attenuated by CB1 blockade. In a mouse model of atherosclerosis, the CB1 antagonist SR141716A (rimonabant) was able to reduce plasma levels of the pro-inflammatory cytokines MCP-1 and IL-12 in low density lipoprotein deficient mice fed with a high fat diet[113]. In addition, rimonabant inhibited lipopolysaccharide (LPS)-induced pro-inflammatory IL-6 and TNF- α expression in mouse peritoneal macrophages *in vitro*. Importantly, this effect was still observed when cells from CB1-knockout mice were used, suggesting a CB1-independent anti-inflammatory effect of rimonabant[113]. In another model of atherosclerosis, Hoyer and co-workers demonstrated a severe vascular leukocyte infiltration in ApoE and CB2 double knockout mice which was more intense than that observed in ApoE-knockout mice[54]. Interestingly, treatment with the selective CB2 agonist JWH-133 decreased leukocyte recruitment in ApoE-knockout mice compared to their wild-type counterparts[54]. In 2010, Zhao *et al*[114,115] showed that treatment with the synthetic cannabinoid WIN55,212-2 reduced atherosclerotic lesion macrophage content and mRNA levels of inflammatory markers IL-6 and TNF- α ; adhesion molecules VCAM-1 and ICAM-1 as well as NF- κ B activation in ApoE-deficient mice fed on high-cholesterol diets. In human coronary artery endothelial cells, activation of CB2 receptors with the selective agonists HU-308 or JWH-133 attenuated the TNF- α -induced NF- κ B activation, ICAM-1 and VCAM-1 up-regulation, MCP-1 release, as well as trans-endothelial migration and adhesion of monocytes, which are hallmarks of the development of atherosclerosis[116].

The beneficial effects of CB2 receptor activation by selective synthetic ligands, such as JWH-133 and HU-308, was largely attributed to decreased endothelial cell activation and suppression of the acute inflammatory response in animal models of myocardial ischemia/reperfusion injury, which are characterized by a rapid increase in cytokines and chemokines in addition to an enhanced influx of leukocytes into the vulnerable region. Attenuated expression of adhesion molecules, chemokine secretion, leukocyte chemotaxis, adherence to endothelium, stimulation of trans-endothelial migration, and linked oxidative/nitrative stress associated with reperfusion damage were all beneficial effects of CB2 receptor

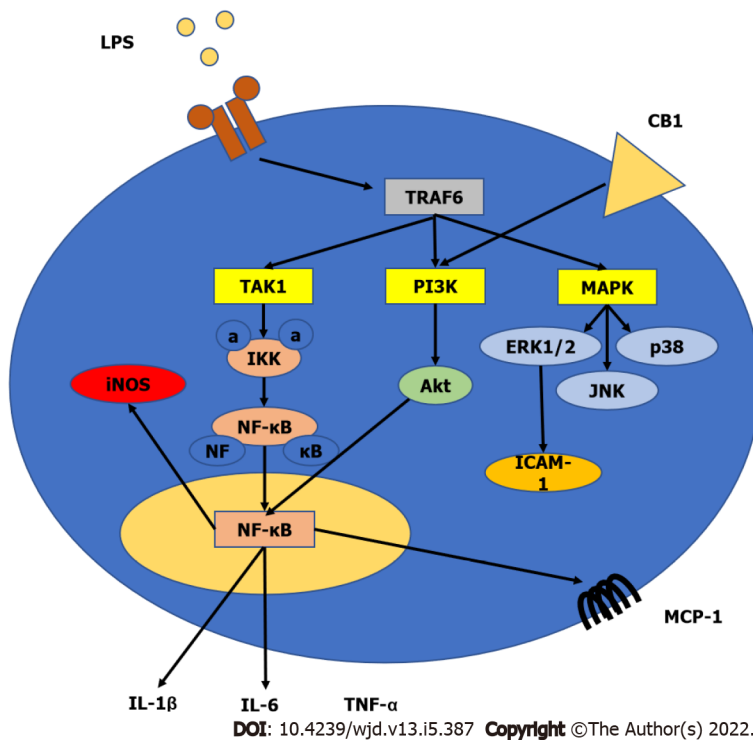


Figure 3 Role of cannabinoid receptors in inflammation. Activation of toll-like receptor 4 induces tumor necrosis factor receptor associated factor 6, which activates transforming growth factor beta-activated kinase 1 (TAK1), phosphoinositide 3-kinase (PI3K), and mitogen-activated protein kinase signaling. This will induce the formation of nuclear factor-kappa B (NF-κB) and the subsequent increase in inflammatory cytokines levels such as interleukin 6 (IL-6), IL-1β, and tumor necrosis factor α (TNF-α) in addition to the activation of inducible nitric oxide synthase (iNOS) and monocyte chemoattractant protein-1 (MCP-1). Stimulation of cannabinoid receptors will increase the PI3K activity leading to increased activity of protein kinase B (Akt/PKB), which in turn enhances the nuclear translocation of NF-κB. TLR4: Toll-like receptor 4; TRAF6: Tumor necrosis factor receptor associated factor 6; PI3K: Phosphoinositide 3-kinase; MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor-kappa B; IL: Interleukin; TNF-α: Tumor necrosis factor α; MCP-1: Monocyte chemoattractant protein-1.

activation[56,117].

In a mouse model of streptozotocin-induced diabetic cardiomyopathy, which is characterized by up-regulation of the expression of various inflammatory cytokines in the myocardium, genetic deletion, or pharmacological blockade of CB1 receptors resulted in attenuation of the expression of: Inflammatory cytokines such as TNF-α and IL-1β, adhesion molecules such as ICAM-1 and VCAM-1, iNOS, and cyclooxygenase 2 (COX2)[92]. In another study using the same model of diabetic cardiomyopathy, it was shown that there was a marked phosphorylation of the inhibitor of NF-κB (IκB-α) in the cytosol of diabetic hearts, leading to the release of the active p65 subunit of NF-κB, which subsequently translocated to the nucleus to induce the expression of inflammatory and apoptotic genes[95]. Treatment with CBD, the non-psychoactive cannabinoid, inhibited the IκB-α phosphorylation and subsequent p65 NF-κB nuclear translocation. The CBD treatment also inhibited the NF-κB-dependent mRNA and/or protein expression of adhesion molecules (ICAM-1 and VCAM-1), the pro-inflammatory cytokine TNF-α, and iNOS in the diabetic myocardial tissues. Cannabidiol (CBD) was also able to attenuate high glucose-induced NF-κB activation in primary human cardiomyocytes[95] (Table 2).

Accumulation of AGEs

An important consequence of high glucose-induced cellular injury is the formation of AGEs. AGEs are a heterogeneous group of compounds formed by the non-enzymatic glycation reaction of glucose and other glycation compounds with proteins and, to a lesser extent, lipids, and DNA[118]. In addition, AGEs can easily make covalent cross-linkages (adducts) with macromolecules like proteins and, in this way, can change the structure and function of these proteins[119]. In diabetic patients, the rate of formation of AGEs is increased. Thus, over time, even modest hyperglycemic excursions can result in significant adduct accumulation in long-lived macromolecules[120]. It is now well established that AGEs interact with cell surface receptors and binding proteins to evoke varied downstream responses. These include the pro-inflammatory responses that could play a critical role in the pathogenesis of diabetic complications including cardiomyopathy[121]. The receptor for AGEs (RAGE) is the most established and the best characterized AGE binding protein[122]. The RAGE is a trans-membrane receptor that belongs to the immunoglobulin super-family and is constitutively expressed in a range of tissues including neurons, endothelium, smooth muscle, epithelium, and inflammatory cells[123].

There are two basic methods by which AGEs might alter myocardial function. AGEs, for starters, can form covalent adducts with proteins including collagen, laminin, and elastin[118,124]. As shown in the myocardium of an animal model of type 2 diabetes, this can inhibit collagen degradation, resulting in collagen buildup and fibrosis, producing increased myocardial stiffness, and reduced ventricular relaxation[19]. Second, soluble extracellular AGEs can bind to RAGE, causing up-regulation of transforming growth factor- β (TGF- β) and NADPH oxidase, resulting in the generation of substantial quantities of cytoplasmic and extracellular superoxide, which can then interact with NO to produce RNS[118]. Furthermore, when the RAGE receptor is active, it promotes the transcription factor NF- κ B and associated genes by elevating intracellular free radical levels and by triggering multiple other signaling pathways[125].

In the literature, little is known about the interaction of the endocannabinoid system and the AGE and/or RAGE. In a mouse model of streptozotocin-induced diabetic cardiomyopathy, genetic deletion of CB1 receptors attenuated accumulation of AGEs and the expression of RAGE in the myocardium of diabetic mice[92] (Table 2).

Myocardial remodeling

Diabetes has a multifactorial nature, therefore there are changes at the cellular and molecular levels that predispose the heart to pathological, structural, and functional remodeling[4]. Diabetic cardiomyopathy is characterized by an unusually increased left ventricular mass and myocardial fibrosis. Left ventricular hypertrophy has been associated with hyperinsulinemia, insulin resistance, increased non-esterified fatty acids, and activation of the renin-angiotensin-aldosterone system[82]. Chronic cardiac remodeling and structural alterations are promoted by a continual cycle of increased ROS production[126,127]. Diastolic dysfunction is defined as an elevation in ventricular wall stiffness and prolonged diastolic relaxation time, and it is common in the early stages of cardiomyopathy[128].

Increased triglyceride buildup and decreased calcium absorption have been linked to diastolic dysfunction[128]. The progression of systolic dysfunction is marked by dilated cardiac remodeling, which leads to heart failure[129]. Cardiomyocyte mortality is accompanied by fibroblast replacement, which leads to interstitial fibrosis driven predominantly by TGF- β [130]. Cardiomyocyte death is mediated by activation of various stress signaling pathways and consequent apoptosis. The deleterious effect of accumulating free fatty acids on mitochondrial biogenesis eventually leads to mitochondrial apoptosis and lowered ATP generation, which is insufficient to meet cardiac demands, resulting in impaired cardiac contractility and lowered ejection fraction[128]. Myocardial dysfunction is caused by impaired endothelial function linked with insulin resistance[13].

Cannabinoid receptors are believed to have the ability to control apoptosis since they may signal through both pro- and anti-apoptotic pathways. Due to the lipophilic nature of their structures, they may be able to operate intracellularly without the help of a membrane transporter[131]. A number of cannabinoid drugs, including HU-210, THC, and anandamide, have been demonstrated to reduce cardiac mitochondrial O₂ consumption in rats[132], as well as the role of mitochondria in marijuana-induced cell death[133]. Stimulation of CB1 receptors by endocannabinoids has also been linked to the activation of signaling pathways (*e.g.*, p38 and JNK-MAPKs) and cell death in various clinical circumstances[51,134]. It is reasonable to conclude, based on earlier results and observations of reduced cardiac apoptosis in FAAH-null animals, that endocannabinoids have strong potential for the regulation of apoptosis, and hence remodeling, in the heart[135].

Doxorubicin treatment is linked to increased anandamide levels in the myocardium, but not to alterations in CB1 or CB2 receptor expression[52]. Doxorubicin triggered apoptosis in a cardiac cell line (H9c2) that was reduced by CB1 receptor blockage, but the result was not sensitive to a CB2 blocker or CB1 and CB2 receptor agonists[52]. Similarly, studies on cardiac function suggest that endocannabinoids have a role in cirrhosis-related cardiac dysfunction[136]. AM251, which blocks CB1 receptors, enhanced cardiac function in rats with carbon tetrachloride-induced cirrhosis, and anandamide levels were shown to be elevated in the hearts of cirrhotic rats compared to controls[137]. In contrast, aging-associated cardiac dysfunction is reduced in FAAH-null mice, which could be interpreted as showing a need for increased endocannabinoid activity in the heart[135].

Mukhopadhyay *et al*[90] demonstrated that genetic deletion of CB1 receptors attenuated cardiac dysfunction induced by doxorubicin in mice. In this study, doxorubicin-induced activation of stress signaling pathways (p-38 and JNK/MAPKs) with subsequent apoptosis was attenuated in CB1 knockout mice. In addition, these findings were supported *in vitro* in human primary cardiomyocytes as the activation of CB1 receptors by anandamide or HU210 resulted in increased activation of p38 and JNK/MAPK, followed by cell death, which are effects that were attenuated by both selective CB1 antagonists (SR141716A or AM281) and MAPK inhibitors[90]. Furthermore, doxorubicin-induced MAPK activation and cell death in human cardiomyocytes were significantly enhanced when doxorubicin was co-administered with anandamide or HU210, an effect which could also be attenuated by both CB1 antagonists and MAPK inhibitors[90]. Another aspect of doxorubicin-induced cardiotoxicity is the induction of myocardial fibrosis, an effect that was attenuated by genetic deletion of CB1 indicating its role in this model of cardiotoxicity[90]. In another study using the same model of doxorubicin-induced cardiotoxicity in mice, it has been shown that FAAH knockout mice exhibited significantly increased doxorubicin-induced cardiac dysfunction and myocardial cell death compared to

their wild-type counterparts. The effects of doxorubicin in FAAH knockouts were attenuated by CB1 receptor antagonists[91].

Acute myocardial infarction causes cardiomyocyte necrosis, which triggers repair mechanisms that result in scarring[138]. This post-infarction cardiac remodeling process involves adaptive changes in the ventricular shape, size, and function, which can lead to contractile dysfunction and heart failure[138]. In ischemic cardiomyocyte death, fibrosis, and cardiac dysfunction, Defer and coworkers showed considerable evidence for the protective impact of CB2 receptors[139]. CB2-knockout mouse hearts displayed larger infarcts and more persistent cell loss 3 d after ischemia, as well as accelerated damage and apoptosis in the non-ischemic remote myocardium compared to wild-type mice[139]. Cardiomyocytes and fibroblasts lacking CB2 were more vulnerable to oxidative stress-induced cell death *in vitro*. Long-term effects of cardiac remodeling in CB2-knockout hearts involved marked fibrosis, accelerated cardiomyocyte hypertrophy, dilated cardiomyopathy, and cardiac dysfunction, as reported 4 wk post-infarction[139]. On other hand, wild-type post-ischemic hearts acquired mild fibrosis and cardiomyocyte hypertrophy while maintaining cardiac function[139]. Wagner and colleagues revealed another investigation where the administration of the CB1 antagonist AM251 for 12 wk after an experimentally induced infarction exacerbated the decline in left ventricular function, but administration of the non-selective cannabinoid agonist HU-210 improved left ventricular performance[140].

A previous study conducted by Liao and co-workers demonstrated that CB1 deficiency contributed to the exacerbation of chronic cardiac remodeling induced by pressure overload in mice, revealing a new role of CB1 in the pathophysiology of congestive heart failure[141]. Genetic deletion of CB1 was found to worsen left ventricular hemodynamics and exacerbate cardiac hypertrophy compared to wild-type mice. Furthermore, it was found that CB1 deficiency led to enhanced activation of the epidermal growth factor receptor, p38, and ERK/MAPKs, which contributed to the exacerbation of cardiac hypertrophy [141].

In patients with chronic heart failure, clinical data revealed an increase in cardiac CB2 expression as well as increased levels of the endocannabinoids, anandamide, and 2-AG[142]. Additionally, in these patients, cannabinoid receptor expression was also found to be slightly downregulated[142]. It was believed that CB2 up-regulation could have a negative inotropic effect due to lower cyclic adenosine monophosphate (cAMP) levels, which could lead to ventricular weakness. CB2 receptors, on the other hand, may mediate positive inotropic effects *via* cAMP-independent processes, hence serving as a compensation strategy to sustain heart function[53]. Furthermore, as demonstrated in rats, CB2 upregulation could be a protective response to counteract structural alterations caused by chronic heart failure [139]. Recently, it has been shown that in biopsies collected from the hypertrophic myocardium of patients with aortic stenosis, there were elevated concentrations of anandamide, higher expression of its degrading enzyme FAAH, and of CB2 receptors[143].

Rajesh *et al*[92] indicated that myocardial dysfunction induced in a mouse model of diabetic cardiomyopathy was improved in CB1-knockout mice or in diabetic mice treated with CB1 antagonists (SR141716A or AM281). This was demonstrated by improved indices of left ventricular systolic and diastolic dysfunction, ejection fraction, contractility, and ventricular stiffness. In the same study, there was attenuated activity of MAPKs and reduced markers of cell death (activated caspase-3 and chromatin fragmentation) in the myocardium of diabetic CB1-knockout mice and in diabetic wild-type mice treated with the CB1 antagonist (SR141716A). Diabetic mice developed myocardial fibrosis as a structural consequence of diabetic cardiomyopathy, and this was characterized by increased accumulation of collagen and enhanced expression of markers of fibrosis such as TGF- β and fibronectin. Interestingly, these changes were attenuated by genetic deletion or pharmacological blockade of CB1 receptors[92]. In another study using the same model, chronic treatment of diabetic mice with the non-psychoactive CBD attenuated the established systolic and diastolic dysfunction in diabetic mice[95]. In addition, CBD treatment attenuated the activation of stress signaling pathways: p38 and JNK/MAPKs. It also enhanced the activity of the pro-survival AKT pathway in diabetic myocardium. Another beneficial effect of CBD treatment in this model was its ability to decrease the activity of the pro-apoptotic enzyme caspase-3 and to reduce the rate of cell death in diabetic myocardium. Finally, CBD treatment protected diabetic myocardium from the deleterious process of fibrosis by decreasing myocardial collagen content and attenuating the expression of fibrosis markers: TGF- β , fibronectin, and the enzyme matrix metalloproteinase[95] (Table 2).

Autophagy

Autophagy, an essential metabolic process, is a self-degradative and recycling procedure dependent on lysosomes. It targets dysfunctional organelles and long-lived proteins[144,145]. This occurs through the biogenesis of double-membrane vesicles containing cytoplasmic components destined for lysosomal degradation, these vesicles are known as autophagosomes[146]. Autophagosome biogenesis entails nucleation, expansion, and closure of the phagophore (a cup-shaped membrane) thereby sequestering cytoplasmic cargo. This is followed by fusion with endolysosomal compartments to facilitate degradation of the sequestered material[146].

Autophagy is performed by genes called autophagy-related (ATG) genes[147]. The discovery of ATG genes in yeast in the 1990s allowed researchers to identify how autophagy works[148]. Today, 36 ATG proteins have been identified as being particularly significant for autophagy, with 18 of them belonging

to the basic machinery[149]. Through the Unc-51-like kinases, ULK1 and ULK2 (mammalian homologues of ATG1), two protein kinases (mTOR and AMPK) control autophagy in mammals[150]. The ULK kinases are dephosphorylated and activated when autophagy is induced. Beclin-1 (mammalian ortholog of ATG6), which is part of a protein complex, is phosphorylated and activated by the ULK[151]. The active ULK and Beclin-1 complexes translocate to the phagophore, the site of autophagosome initiation, where they both help to stimulate downstream autophagy components[152].

Autophagosome production requires two ubiquitin-like conjugation mechanisms[153]. The first one covalently binds the ubiquitin-like protein ATG12 to ATG5. The conjugate protein subsequently attaches to ATG16L1, forming an E3-like complex that is part of the second ubiquitin-like conjugation system[154]. This complex binds and activates ATG3, which covalently binds to the mammalian homologues of the ubiquitin-like yeast protein LC3 to the lipid phosphatidylethanolamine (PE) on autophagosome surfaces[155]. Lipidated LC3 aids autophagosome closure[156] and facilitates the docking of particular cargos and adaptor proteins such as Sequestosome-1/p62[157]. The autophagosome then unites with a lysosome to produce an autolysosome. The autolysosome's contents are then destroyed, and their constituents are liberated from the vesicle[158].

Autophagy has a role in the control of cardiovascular disorders such as myocardial infarction and atherosclerosis[159]. Increased autophagy levels have been shown to protect against diabetic cardiomyopathy[160,161]. As a result, pharmacological activation of autophagy might be a promising therapeutic strategy for diabetic cardiomyopathy.

Autophagy also plays an essential role in the functioning of a variety of receptors. In the case of cannabinoid receptors, autophagy has been related to the protective effects of CB2 in a variety of disorders[162-164], suggesting the relevance of autophagy in disease treatment. Autophagy was previously shown to contribute to the alleviative effects mediated by CB2 activation in inflammatory disorders such as multiple sclerosis, alcoholic liver disease, and inflammatory bowel disease[162-164]. Activating CB2 improved inflammatory bowel disease in mouse models by inhibiting the NLRP3 inflammasome and triggering autophagy in murine macrophages, according to Ke and colleagues[163]. In mouse multiple sclerosis models, a similar relationship between CB2 and autophagy was discovered [164].

In the case of autophagy in diabetic cardiomyopathy, it was shown that increasing autophagy levels contributed to improving the condition. Several treatments have been demonstrated to be beneficial in reducing the etiology and development of diabetic cardiac myopathy by utilizing enhanced autophagy levels[160,161,165,166]. CB2 activation *via* autophagy induction provided protection against diabetic cardiomyopathy, according to a recent study by Wu and coworkers[167]. They used HU308 to selectively activate CB2, resulting in a substantial increase in autophagy levels in diabetic cardiomyopathy heart tissues *in vivo* and hyperglycemia-challenged cardiomyocytes *in vitro*. Furthermore, inhibiting autophagy with bafilomycin A1 reduced the cardioprotective effect of HU308 in both *in vitro* and *in vivo* models. Wu *et al*[167] concluded that CB2-induced autophagy was involved in the CB2-mediated cardio-protective effect.

Resveratrol, an autophagy inducer, was discovered to have a cardio-protective impact in cardiomyocytes exposed to hyperglycemia *via* the AMPK-mTOR-p70S6K signaling pathway[168]. AMPK-mTOR signaling contributed to the cardio-protective effect in STZ-induced diabetic mice by increasing autophagy[161,169]. According to these findings, Wu *et al*[167] found that administering HU308 to selectively activate CB2 enhanced AMPK phosphorylation while lowering mTOR and p70S6K phosphorylation, initiating the AMPK-mTOR-p70S6K signaling cascade in murine primary ventricular cardiomyocytes. Furthermore, using compound C, an AMPK inhibitor, significantly reduced the cardio-protective effect of HU308, showing that AMPK-mTOR-p70S6K signaling-induced autophagy was essential in CB2-mediated cardiac protection in dilated cardiomyopathy[167]. However, because the mechanisms behind CB2-mediated autophagy activation are complex, more research is required. Figure 4 summarizes the effect of cannabinoid receptors on AMPK/mTORC1/NLRP3 signaling.

Cannabidiol (CBD), has recently gained increased interest for therapeutic use. Indeed, CBD has been shown to suppress a high glucose-induced inflammatory response and barrier disruption of endothelial cells[170] and to attenuate myocardial dysfunction, cardiac fibrosis, oxidative/nitrative stress, inflammation, cell death, and interrelated signaling pathways in a mouse model of type I diabetic cardiomyopathy[95]. The critical role of HO-1 has been evident in the regulation of autophagy, with survival-enhancing effects in various cell types, including endothelial cells[171-173]. Moreover, HO-1 showed positive *in vivo* effects in animal models of atherosclerosis and restenosis[174]. Böckmann and Hinz have recently proved that CBD promoted endothelial cell survival *via* HO-1 mediated autophagy[170] (Table 2).

CONCLUSION

Diabetes-induced cardiomyopathy is a deleterious complication of the cardiovascular system characterized by structural and functional changes in the myocardium that ultimately lead to cardiac failure. The mechanisms underlying the development of diabetic cardiomyopathy are complex and involve several pathogenic pathways. A great body of evidence supported a special role of oxidative/nitrative

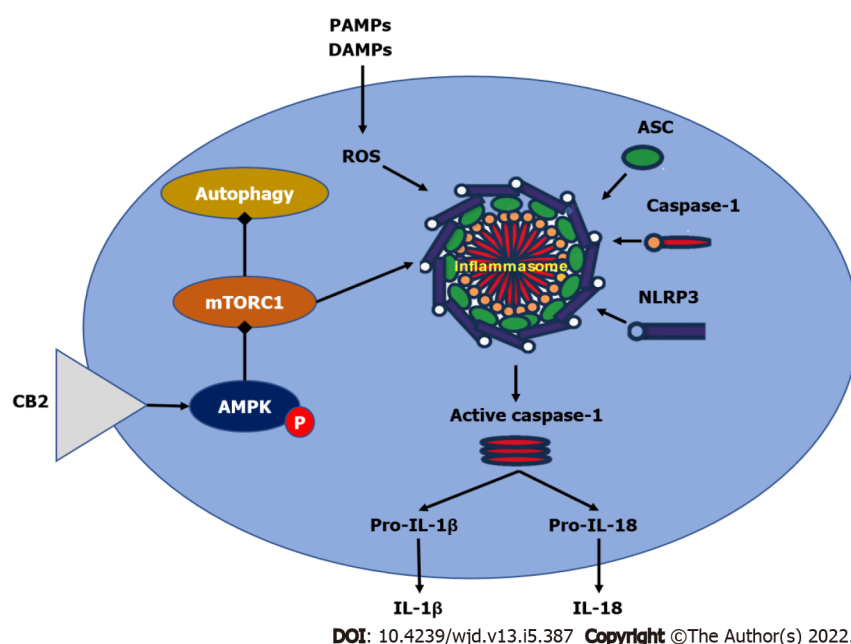


Figure 4 Effect of cannabinoid receptors on adenosine monophosphate activated protein kinase/mammalian target of rapamycin complex 1/NLR family pyrin domain containing 3 signaling. Cannabinoids enhance the phosphorylation of adenosine monophosphate activated protein kinase (AMPK), which reduces the stimulatory effect of mammalian target of rapamycin complex 1 (mTORC1) on inflammasome assembly. Depressed activation of NLR family pyrin domain containing 3 (NLRP3) will diminish the activation of procaspase-1 leading to a decrease in interleukin-1 β (IL-1 β) and IL-18 production. Additionally, the inhibitory effect of phosphorylated AMPK on mTORC1 will enhance autophagy. AMPK: Adenosine monophosphate activated protein kinase; mTORC1: Mammalian target of rapamycin complex 1; NLRP3: NLR family pyrin domain containing 3; IL: Interleukin.

stress and inflammation in the pathogenesis of diabetic cardiomyopathy. The endocannabinoid system has been implicated in the development of several pathological conditions including cardiovascular disorders. Several mechanisms have been proposed as targets by which cannabinoids and the endocannabinoid system could modulate cardiovascular disorders and recent evidence suggested the involvement of this system in the pathogenesis of diabetic cardiomyopathy. Indeed, the manipulation of the endocannabinoid system could represent a promising therapeutic approach for diabetic cardiomyopathy, and several mechanisms have been proposed for this role including its effects on oxidative/nitrative stress, inflammatory pathways, and autophagy together with possible effects on cardiac remodeling. However, more research is needed to define the exact mechanisms of the intervention of the different components of this system in diabetic cardiomyopathy.

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FOOTNOTES

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