Nat. Volatiles & Essent. Oils, 2020; 7(1): 69-76
https://doi.org/10.52783/nveo.5449

NVEO
Natural Volatiles & Essential Oils

Role Of Endocanabinoid System In Diabetes Mellitus

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Abstract

Long-term consequences of diabetes are very harmful and persistent, therefore preventing them requires more than just tight glycemic management. One of the most prevalent fatal effects of diabetes, diabetic cardiomyopathy is the main cause of death in people with diabetes. Type 1 and 2 cannabinoid receptors, in addition to other factors. Nonetheless, research into the endocannabinoid system's potential impact on diabetic cardiomyopathy remains limited. In order to better understand how cannabinoids and the endocannabinoid system may play a role in the etiology and progression of diabetic cardiomyopathy, this review attempts to do so.

Keywords: Cannabinoid; receptors; Diabetic; cardiomyopathy; Endocannabinoid; Inflammation

INTRODUCTION

The prevalence and impact of diabetes mellitus, now among the most prevalent chronic diseases globally, are expected to rise in the coming years. The International Diabetes Federation estimates that 463 million people throughout the world have diabetes, for a global prevalence of 9.3 percent. By 2045, an estimated 700 million people worldwide would be living with diabetes, up from the estimated 578 million in 2030. Four million people died from diabetes-related causes in 2017, and the global cost of treating the disease reached $727 billion that year. Hyperglycemia due to an absolute or relative shortage of insulin characterizes diabetes mellitus, a complicated metabolic condition. Insulin resistance is often associated with this condition.

Fifty years ago, scientists isolated 9-tetrahydrocannabinol (THC), the primary psychoactive compound in Cannabis sativa. Since then, researchers have been working hard to determine the physiological and pathological functions of the endogenous molecules that THC mimics. Signaling occurs through interactions between endocannabinoids (ECs), enzymes that regulate EC production and degradation, and receptors that bind to ECs. Anandamide (AEA), a bioactive lipid mediator, and 2-arachidonoylglycerol (2-AG) have received the greatest attention from researchers. ECs are produced "on demand," with phospholipase D primarily responsible for the hydrolysis of N-arachidonoyl phosphatidylethanolamine to produce AEA, and diacylglycerol lipase (DGL) synthesizing 2-AG from diacylglycerol. Although Gi/o-coupled cannabinoid receptors 1 and 2 play a major role in mediating EC effects, other receptors, such as GPR-55, may also play a role.

The central nervous system has an abundance of CB1 receptors, whereas the immune, inflammatory, and hematological systems are primarily where CB2 receptors are found. However, cannabinoid receptors have been discovered on other cell types as well, and there is growing evidence connecting the endocannabinoid system to a wide range of pathological states. This means that neurodegenerative, cardiovascular, gastrointestinal, hepatic, and renal diseases may all benefit from pharmaceutical modulation of the ECS. We present a short summary of recent research demonstrating the ECS's critical involvement in T2D development and progression. The ECS will be highlighted as a therapeutic target for diabetes and its consequences.

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Endocannabinoid System: An Overview

Endocannabinoids (ECs) and the enzymes responsible for their breakdown and production are only two parts of the complex endogenous cannabinoid system. This system, which emerged throughout evolution and is now ubiquitous, plays a crucial role in maintaining the health of cells and tissues. The term "endocannabinoid" was created immediately after the discovery of endogenous ligands of 9-tetrahydrocannabinol receptors, and refers to lipid-based signaling molecules. Enzymes that catalyze its breakdown or production are also part of the signaling network. Synaptic inhibition is regulated by the well-established EC system, which is one of the main neuro-modulatory systems in the brain. The ECS is essential for controlling energy homeostasis and organ function at the periphery. It increases overall calorie intake by modulating behavior at multiple places throughout the body. ECs are found in triglycerides and membrane phospholipids, and the two most common forms are 2-arachidonoyl glycerol and anandamide.

In contrast to other neurotransmitters, ECs undergo use-dependent production in response to high levels of acute stimulation by increasing intracellular calcium concentration. These enzymes, which may bind and activate CB receptors, are secreted directly from cells after biosynthesis and are necessary for the development of the two kinds of ECs indicated. CB receptors with the molecular features CB1 and CB2 are found only in immune cells and blood. Selective absorption into cells and subsequent enzymatic hydrolysis assist clear extracellular spaces of ECs.

In contrast, pharmaceutical modulations try to restore balance to an overactive EC system, which would theoretically result in less synthesis, a halt in transportation, and more degradation. Understanding the endocannabinoid system's complex signaling mechanism and developing medicines with specific activity is, thus, a significant problem. It also posits the possibility of locating novel medicinal drugs. The physiological role of ECS in a wide variety of disorders may be better understood thanks to the current efforts to identify novel agonists and antagonists with selective receptor binding. This has the potential to promote the research and development of medicines with therapeutic potential for regulating ECS activity (Figure 1).

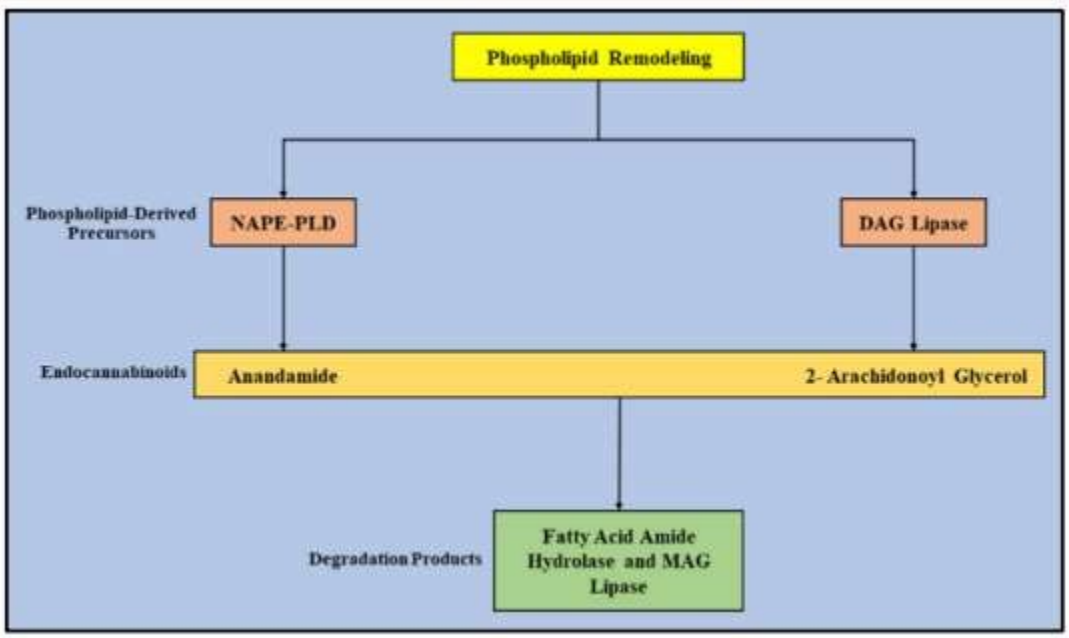

Figure 1. Degradation and production of endogenous cannabinoids by enzymes

There are proteins that control the amount of endocannabinoids in tissue, and endocannabinoids themselves are endogenous ligands for CB1 and CB2 cannabinoid receptors. The potential role of cannabinoids and the

endocannabinoid system in determining the onset and progression of diabetic cardiomyopathy is the topic of this review, Eventually, this device might be used to treat these potentially fatal diabetic complications.

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
Rimonabant (SR141716A)	CB1 antagonist	Reduced weight Reduced hemoglobin A1c levels, Reduced fasting blood glucose levels Reduced high density lipoprotein, cholesterol and triglyceride levels, Improved systolic blood pressure
Δ9-tetrahydrocannabinol (THC)	Psychoactive cannabinoid CB1 partial agonist CB2 partial agonist Non-psychoactive	Lowered blood glucose level; Preserved pancreatic insulin content
Cannabidiol	cannabinoid Low affinity to CB1 and CB2	Reduced the incidence of type I diabetes, Immunosuppressive effect

LITERATURE REVIEW

Dörnyei, G.; Vass, Z.; Juhász, C.B.; Nádasy, G.L.; Hunyady, L.; Szekeres, M. (2019), The onset of metabolic syndrome is often the end result of poor diet and lack of physical activity. Insulin resistance (IR), diabetes, dyslipidemia, hypertension, and atherosclerosis are all examples of metabolic problems that lower quality of life and shorten a person's lifespan. The endocannabinoid system (ECS) is involved in signal transduction activities both centrally and in the periphery. Overexpression or downregulation may have a negative impact on several physiological processes and lead to a variety of illnesses. Through analysis of ECS roles in physiological and pathological processes, we describe many novel signaling pathways implicated in the etiology of metabolic syndrome. This study highlights how the recent discovery of ECS signaling stages like these opens up exciting new therapeutic possibilities for treating metabolic illnesses including diabetes, insulin resistance, obesity, and hypertension.

V. Di Marzo (2018), The EC signaling system consists of ECs, cannabinoid receptors, and anabolic and catabolic enzymes. It seems that energy storage as fat may be the ultimate goal of this system, given its function in regulating lipid and glucose metabolism at several levels. Energy balance depends on a number of organs, most notably the adipose tissue located inside the abdominal cavity, become dysregulated and, in most instances, hyperactive after an imbalanced energy intake. Several cardiometabolic risk factors, such as increased visceral fat accumulation and reduced adiponectin synthesis from this tissue, have been related to this imbalance.

Medapati, J.R., Rapaka, D., Bitra, V.R. et al. (2019), The purpose of this research is to learn more about how CB1 receptors may play a role in the onset of diabetic nephropathy. Streptozotocin (STZ) is administered intraperitoneally (i.p.) to non-inephrectomized rats to cause diabetes mellitus in a laboratory setting. Diabetic rats received a CB1 agonist and an antagonist for 24 weeks, beginning 1 week after STZ injection.

Researchers Chwalba and Otto-Buczkowska (2019) It seems to serve a crucial function in controlling hormone secretion. Endocannabinoid receptors are crucial parts of this system (types CB1 and CB2). Many peripheral tissues, as well as the brain and spinal cord, have endocannabinoid receptors. The islands of Langerhans are another common site for them. The endocannabinoid system is involved in endocrine secretion control in the human pancreas. Glucose metabolism in muscle cells and lipid production and turnover in the liver and adipose tissue are only a few of the processes that the endocannabinoid system controls.

Vähätalo, Ruohonen, Mäkelä, et al., 2015. Endocannabinoids and neuropeptide Y (NPY) are involved in both central and peripheral pathways that aid in the storage of energy. It was hypothesized that the hypothalamus would serve as a relay for information between the two networks. To further understand this connection outside of the hypothalamus, we examined endocannabinoid levels in the sympathetic nervous system and brains of obese OE-NPYDH mice.

Diabetes and diabetic complications

It is estimated that by 2035, 592 million people would be living with diabetes mellitus, up from the current 387 million. The proliferation of type 2 diabetes has been connected to the rise in obesity rates. Effective weight control has been shown to prevent almost 80% of occurrences of type 2 diabetes. There are many different issues that may arise from having diabetes, which is why it is the seventh biggest cause of mortality in the United States, including macrovascular and microvascular issues. Diabetics have two to six times the risk of developing macrovascular complications.

MODULATE DIABETIC CARDIOMYOPATHY

The mitochondrial superoxide (O2-) radical is the primary oxygen free radical generated, and it uses around 5% of the oxygen supplied to tissues. The remaining 95% is used in metabolic activities to produce adenosine triphosphate (ATP). Superoxide dismutase are antioxidant enzymes that catalyze the rapid intracellular conversion of superoxide to hydrogen peroxide (H2O2). Rapid reactions between superoxide radicals and nitric oxide (NO) result in both hydrogen peroxide (H2O2) and the deadly peroxynitrite anions (ONOO-). When combined with carbon dioxide, peroxynitrite is more reactive than superoxide and NO and may cause protein breakdown and lipid oxidation.

In the diabetic myocardium, ROS cause cell damage via many pathways. Increasing ROS cause immediate harm to proteins and DNA in cells. Contractile tissue is lost due to cardiac hypertrophy and cardiomyocyte death. Similar to nitric oxide, peroxynitrite may cause vasoconstriction, increased leukocyte adhesion, platelet activation, oxidation, a pro-thrombotic state, poor coagulation, and vascular inflammation, all of which can contribute to atherosclerosis. Type 1 diabetic mice provided further evidence that mitochondrial reactive oxygen species (ROS) play a role in the development of cardiac abnormalities by demonstrating that specific suppression of ROS in the mitochondria prevented diabetic cardiac deficits. In addition, Rac1 contributes to cardiomyocyte mortality and heart failure in mice with streptozotocin-induced diabetes via increasing mitochondrial ROS production through NADPH oxidase activation.

Ablation of CB1 receptors genetically protected animals against the cardio-toxic effects of the anticancer

medication doxorubicin, which causes an increase in oxidative and nitrative (nitrotyrosine) stress indicators in the myocardium when administered in high quantities. Myocardial glutathione, glutathione peroxidase, and superoxide dismutase (SOD) levels dropped following doxorubicin treatment. CB1 knockout mice had reduced myocardium changes. CB1 antagonists, such as SR141716A or AM281, mitigated the adverse impact.

Cannabinoids prevented maladaptive changes in heart and vascular structure and function and corrected changes in lipid peroxidation and oxidative stress indicators in 2017 research by Vella et al. CBD administration to diabetic C57BL/6J mice for 11 weeks was shown to diminish cardiac lipid peroxidation, protein carbonyl production, and reactive oxygen species (ROS). Cannabinoids have the potential to increase NO bioavailability via their association with the anandamide binding site, which has been linked to NO release. By restoring redox equilibrium, THC enhanced cardiac and vascular end-organ function in STZ-induced diabetic mice. The endothelium-dependent relaxation of resistance arteries and the maintenance of normal cardiac electrophysiology are all indicators of this. These findings suggest that cannabinoid receptor activation in a diabetic cardiomyopathy animal model is a prospective pharmacological target. (Table 2).

Table 2 Modulation of Diabetic Cardiomyopathy

Cannabinoid agent	Mechanism	Effect
Endocannabinoids	Oxidative/Nitrative stress	Influenced ROS and RNS production Triggered activation of signaling pathways (*e.g.*, p38 and JNK-MAPKs), promoting cell death
	Myocardial remodeling	Increased during inflammation Modulating T and B lymphocyte proliferation and apoptosis, inflam- matory cytokine production and immune cell activation by inflammatory stimuli
	Inflammation	
AM281 SR141716A	Oxidative/Nitrative stress	Attenuated doxorubicin-induced oxidative stress
	Oxidative/Nitrative stress	Attenuated doxorubicin-induced oxidative stress
	Inflammation	Reduced plasma levels of the pro-inflammatory cytokines MCP-1 and IL- 12 in low density lipoprotein deficient mice Inhibited LPS-induced pro-inflammatory IL-6 and TNF-α expression
	Myocardial remodeling	Reduced activation of p38 and JNK/MAPK Improved myocardial dysfunction induced in a mouse model of diabetic cardiomyopathy Reduced markers of cell death (activated caspase-3 and chromatin fragmentation)

JWH133	Oxidative/Nitrative stress	Reduced ROS release in ApoE knockout mice
	Inflammation	Decreased leukocyte recruitment in ApoE-knockout mice Attenuated TNF-α-induced NF-κB activation Attenuated ICAM-1 and VCAM-1 up-regulation
Cannabidiol	Oxidative/Nitrative stress	Attenuated oxidative and nitrative stress in the myocardium of strepto-zotocin-induced diabetic mice Prevented changes in markers of lipid peroxidation and oxidative stress in diabetic rats
	Inflammation	Inhibited IκB-α phosphorylation and subsequent p65 NF-κB nuclear translocation Attenuated high glucose-induced NF-κB activation in primary human cardiomyocytes
	Myocardial remodeling	Attenuated the established systolic and diastolic dysfunction in diabetic mice Attenuated the activation of stress signaling pathways: p38 and JNK/MAPK Enhanced the activity of the pro-survival AKT pathway in diabetic myocardium Decreased the activity of the pro-apoptotic enzyme caspase-3
	Autophagy	Promoted endothelial cell survival *via* HO-1 mediated autophagy
Anandamide	Oxidative/Nitrative stress	Induced NO bioavailability
	Myocardial remodeling	Decrease rat heart mitochondrial O_2 consumption Increased activation of p38 and JNK/MAPK, followed by cell death Enhanced doxorubicin-induced MAPK activation and cell death
Δ9-tetrahydrocannabinol (THC)	Oxidative/Nitrative stress	Regulated redox state in diabetic rats
	Myocardial remodeling	Decreased rat heart mitochondrial O_2 consumption
WIN55, 212-2	Inflammation	Reduced atherosclerotic lesion macrophage content and IL-6 and TNF-α levels Reduced adhesion molecules VCAM-1 and ICAM-1 as well as NF-κB activation

Diabetic cardiomyopathy

Several enzymes involved in EC production and metabolism, as well as essential cannabinoid receptors, are found in the cardiovascular system. Preclinical research suggests that the ECS has a negligible effect on cardiovascular control under normal physiological settings. Yet, its importance in the development of cardiovascular disease has only been apparent lately. (Pacher et al., 2006). CB1 and CB2 receptor activation seem to have opposite outcomes in most important cardiovascular diseases, similar to the DN described above. (Pacher et al., 2006). Moreover, ECs may stimulate profibrotic signaling in fibroblasts/myofibroblasts and ROS production in murine and human cardiomyocytes, endothelium, and smooth muscle cells via CB1 receptor-dependent/independent pathways.

In line with this, a connection between ECs and CB1 receptors and the onset of shock has been shown, heart

failure, and atherosclerosis through their roles in cell death and inflammation (Pacher et al., 2006). CB2 receptor activation, on the other hand, inhibits immune cell activation, chemotaxis, and inflammatory cell adherence to active endothelium. Moreover, CB2 receptor stimulation inhibits smooth muscle proliferation, reduces endothelial cell activation and pro-inflammatory response, and may have cardioprotective benefits (Steffens and Pacher, 2012). The beneficial effects of CB2 receptor agonists shown in models of ischaemic/reperfusion damage in the heart and brain may be attributed to these mechanisms (Pacher and Hasko, 2008). Concerns about the specificity of the commercially available CB2 receptor antibodies make it necessary to validate the involvement of CB2 receptors in cardiomyocytes in more detail.

Rajesh et al. (2012) Researchers discovered elevated AEA and CB1 receptor expression in the hearts of diabetics, which correlated with higher AGE buildup, inflammation, cell death, fibrosis, and oxidative/nitrosative stress. In a model of type I diabetes, blocking CB1 receptors prevented and reversed pathological remodeling and diabetic cardiac dysfunction, but this effect was glucose-independent. Chronic CB1 receptor blockade in db/db mice, like its previously observed favorable effects in DN, reduced cardiac fibrosis and remodelling (Nam et al., 2012).

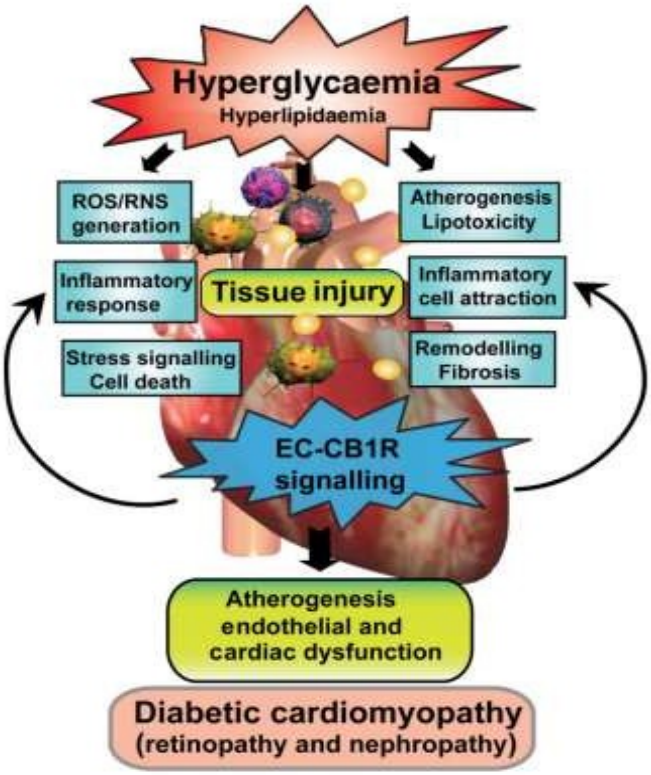

Figure 2 Role of the EC-CB1 receptor signalling in diabetic cardiovascular complications.

CONCLUSION

Treatments based on cannabinoids show promise in preventing diabetes complications. Despite a paucity of evidence on the functional significance of this mutation in the receptor gene, recent studies have linked a common CB1 receptor polymorphism to an increased risk of developing nephropathy and retinopathy in type 2 diabetics. (Buraczynska et al., 2014). Consequently, it seems that antagonists of the CB1 receptor of the second generation may be useful in the treatment of diabetes problems. In conclusion, cannabidiol and other components of marijuana have shown promise as possible therapies for diabetes and diabetic complications.

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