

Review of the Effect of Cannabidiol on the Vascular System

Andrew Schiro*, Uzma Sadia and Arun Pherwani

Department of Vascular, Royal Stoke University Hospital, Stoke-on-Trent, UK

*Corresponding author: Andrew Schiro, Department of Vascular, Royal Stoke University Hospital, Stoke-on-Trent, UK, Tel: +4407716391419; E-mail: andrew.schiro@nhs.net

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Abstract

The effects of cannabinoids are mediated by G-protein coupled cannabinoid receptors 1 (CB1) and 2 (CB2). CB1 is mainly present in the vascular and central nervous system whilst CB2 receptors are found within the immune tissues that are involved in immunomodulation. There is emerging evidence to suggest that the endocannabinoid system plays an important role in regulating the cardiovascular system. This review focuses on the therapeutic potential of Cannabidiol (CBD) on the cardiovascular system.

Keywords: Endocannabinoid; Cardiovascular system; Immunomodulation

[8,9]. The two cannabinoid receptors are G-protein- coupled receptors that are found in various sites within the body [10]. The CB1 infarction, hypertension and cerebrovascular disease [8]. The two cannabinoid receptors are G-protein- coupled receptors that are found in various sites within the body. The CB1 receptor is responsible for the behavioural properties associated with cannabinoids and is expressed within the central, peripheral nervous systems as well as the vascular, endocrine, digestive and reproductive systems maintaining homeostasis in health and disease [11,12]. CB2 receptor is found within the immune tissues and is involved in immunomodulation.

The endocannabinoid system is involved in several physiological processes. Endocannabinoids are mainly produced in the central nervous system regulating pain, motor function, stress responses as well as reproductive function. Synthesis and function of endocannabinoids also takes place in peripheral tissue such as vascular system, GI tract, muscle, pancreas, liver where they exert inflammatory responses and act on vasculature by modulating blood pressure, heart rate and platelet function [13,14]. Their involvement in many physiological aspects makes them attributable to several disease processes such as cardiovascular disorders, diabetes, inflammatory conditions and cancer.

Introduction

The medicinal and recreational properties of the plant *Cannabis sativa* L have been known for centuries. *Cannabis sativa* L is known to contain over a hundred compounds known as cannabinoids [1]. Tetrahydrocannabinol (THC) was one of the first cannabinoids to be extracted and researched by Mechoulana et al. for its psychoactive properties on the central nervous system [2]. Most of the effects of THC are attributed to the activation of the cannabinoid receptors CB1 and CB2 receptors present in mammalian tissues [3]. The discovery of these two receptors led to the discovery of their endogenous agonists, the endocannabinoids N-Arachidonyl Ethanol Amine (AEA) and 2-arachidonoyl glycerol (2-AG) that constitute the endogenous Endocannabinoid System (ECS) [4,5]. The ECS also includes enzymes that are involved in the biosynthesis and inactivation of endocannabinoids [6]. N-acylphosphatidylethanolamine-specific phospholipase D and diacylglycerol lipase are involved in the biosynthesis of AEA and 2-AG respectively whilst Fatty Acid Amide (FAAH) and Monoacyl Glycerol Lipase (MAGL) are involved in the hydrolysis of AEA and 2-AG [7].

The Endocannabinoid System

Over the years research has shown that targeting of the endocannabinoid system can be used to treat a variety of disorders such as cardiovascular disease including myocardial infarction, hypertension and cerebrovascular disease

Cardioprotective Effects of Cannabidiol

Cannabidiol (CBD) is a non-psychoactive phytocannabinoid that is similar to THC which acts on the CB1 and CB2 receptors [15]. CBD has been shown to have therapeutic potential in a variety of disorders including inflammation, diabetes, vascular disease, gastrointestinal and neurodegenerative disorders [16,17]. There is increasing evidence that shows the positive effects that CBD has on the vascular system and its potential clinical use. CBD appears to be well tolerated in humans and is commercially available as Sativex® which is a combination of THC and CBD. Cannabinoid compounds have been studied in the acute vascular setting with *in vivo* and *in vitro* models showing vasorelaxation of vessels [18]. Studies have also shown that endocannabinoids also act as mediators of myocardial infarction as well as ischaemic reperfusion injury and atherosclerosis [19,20]. The precise pharmacological effect of CBD has not been elucidated however several studies demonstrate its anti-inflammatory and anti-apoptotic effects which confer tissue protection [21]. Durst et al. have demonstrated that

administration of CBD reduced myocardial infarct size several days following ischaemic/reperfusion injury due to profound anti-inflammatory effect as a result of reduced infiltration of inflammatory cells and interleukin-6 into the myocardium [22]. Similarly Walsh et al. have demonstrated that CBD is cardioprotective in the acute phase reducing ventricular arrhythmias and attenuating infarct size [23]. These data suggest that treatment with CBD has significant cardioprotective effect on the heart *via* its anti-inflammatory mechanisms.

Haemodynamic and Anti-Inflammatory Effect of Cannabidiol

CBD is a well-known anxiolytic, reducing the cardiovascular response to stress and anxiety. Resstell et al. have demonstrated a reduction in heart rate and blood pressure in lab rats subjected to fear and stress when a small dose of CBD was administered [24]. It is presumed that the inhibitory effect of CBD on the cardiovascular system is responsible for this. CBD could potentially be used in the treatment of stress in humans and possibly reduce the harmful effects of hypertension and atherosclerosis [25].

There is a strong evidence to suggest that treatment with CBD may improve conditions associated with endothelial dysfunction such as diabetes. Diabetic patients tend to have high serum glucose concentrations responsible for the disruption of the endothelial nitric oxide regulatory mechanism, increased superoxide production as well as constrictor prostaglandins. Furthermore, leucocyte adhesion and monocyte migration into the endothelium are more pronounced in these patients [26]. Prolonged exposure to high glucose concentration has also been shown to increase adhesion molecules such as ICAM-1 and VCAM-1 in coronary endothelial cells and disrupt the endothelial barrier as well as mitochondrial superoxide production. Rajesh et al have demonstrated a reduction of these harmful effects following the administration of CBD. CBD was shown to decrease monocyte adhesion and translocation which are key elements in the formation of atherosclerosis [27].

Neuroprotective Effect of CBD in Stroke

The neuroprotective effect of CBD as well as endogenous cannabinoids has been demonstrated *in vivo* and *in vitro*. Hampson et al were the first to show that rats subjected to middle cerebral artery occlusion and treated with CBD had a reduction in infarct size and neurological impairment [28]. Similarly administration of CBD following a stroke protected against neuron damage. Following an ischaemic stroke, cerebral blood flow is diminished however when CBD was administered cerebral laser doppler measurements have shown an improvement in blood flow suggesting that CBD is neuroprotective [29,30].

Conclusion

This review has presented positive evidence of the effects of CBD on the cardiovascular system. *In vivo* CBD administration is protective at reducing cardiac ischemia and reperfusion injury as

well as diminishing the damaging effects of diabetes and formation of atherosclerotic plaques in the body. Similarly, CBD is protective in stroke models due to its vasodilatory effects that help maintain the cerebral perfusion pressures. These data suggest that the human cardiovascular system is potentially a good therapeutic target.

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