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Cannabinoids and Endothelial Dysfunction

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ABSTRACT

Over the past 50 years, the recreational use of *Cannabis sativa* increased enormously, especially in the young population. The main psychoactive and euphoric effects of *Cannabis sativa* are due to Δ-9-tetrahydrocannabinol. Once cannabinoid receptors, CB1 and CB2, were discovered to be distributed in the cardiovascular system, this was the starting point to assess the effects of *Cannabis sativa* on vascular endothelium. The aim of this review is to focus attention on the role of cannabinoids in endothelial dysfunction. The CB1 receptor seems to have a pro-atherogenic profile while the CB2 receptor acts to counteract the onset of atherosclerosis. In addition, several lines of evidence (e.g., epidemiological studies, clinical trials and animal studies) correlate marijuana smoking to a worsening of angina pectoris and the onset of acute coronary syndromes. It has been demonstrated that endothelial dysfunction plays a crucial role in the pathogenesis and progression of atherosclerosis. Cannabinoids and their receptors can play an important role in the alterations of endothelial function and morphologies, thus in the advance of atherosclerotic process.

Key words: Cannabinoids, CB1 and CB2 receptors, endothelial dysfunction, atherosclerosis

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INTRODUCTION

The use of *Cannabis sativa* dates back to about 4000 years ago when it was adopted for its euphoric effects[1]. However, over the last 50 years, the recreational use of *Cannabis sativa* increased enormously, especially in the young (15-35-year-olds). According to the National Survey on Drug Use and Health, marijuana is the most used drug in the United States[2]. Many studies in the literature demonstrated the clinical effects of cannabinoids on the cardiovascular system[3,4,5,6,7,8]. Following the recent debates over *Cannabis sativa* by-product legalization and increases in use, it is critical to examine the role of cannabinoids in endothelial dysfunction.

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Biochemical background: Several chemical compounds have been isolated from *Cannabis sativa* but the numerous pharmacological properties of the plant are attributed to Δ-9-tetrahydrocannabinol (Δ-9-THC). Δ-9-THC is the main component of *Cannabis sativa* isolated in 1967 by Mechoulam and Gaoni[9] and the main psychotropic molecule. Based on the percentage content of Δ-9-THC, it is possible to distinguish three main forms of cannabis: Marijuana (contains 0.5-5% of Δ-9-THC), hashish (contains 2-20% of Δ-9-THC) and cannabis oil (contains 15-50% of Δ-9-THC)[10]. Two different membrane receptors for THC were discovered, called CB1 and CB2 through molecular cloning[11]. They are ubiquitous and localized in different proportion in tissue. CB1, in particular, is expressed in the brain and other peripheral tissues like heart and vascular endothelium, vascular smooth muscle cells, liver,

gastrointestinal tract and kidneys[12,13]. Initially, CB2 receptor was estimated to be expressed exclusively by cells of the immune system[14]. Further studies identified CB2 receptor also in the vascular endothelium where it plays an anti-inflammatory action[15].

These receptors are also targets of cannabinoid-like, endogenous substances called endocannabinoids. Currently two endogenous cannabinoids were identified: Anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG)[4].

Clinical effects of cannabinoids: The increase in the use of *Cannabis sativa*, is due to the euphoric effects like euphoria, relaxation, alteration of sensory perception with distortion of the sense of time and intensification of everyday experiences induced by its constituent chemical compounds[16]. This euphoric perception corresponds to a Δ-9-THC's blood concentration of about 2 μg L^{-1} [17]. The use of *Cannabis sativa* in a social context makes the consumer more cheerful, sociable and talkative even the negative effects of *Cannabis sativa* are often amplified by cultural and socio-demographic factors in habitual consumers[18]. To achieve the desired psychoactive effects of *Cannabis sativa,* inhalation is the preferred way of administration. After smoking a "Standard" dose of *Cannabis sativa* (usually around 20 mg), the blood concentration of Δ-9-THC rapidly rises reaching the nadir even before the end of the inhalation. The Δ-9-THC concentration detected in the lungs varies from 20-70%, while the one that reaches the brain is between 5-24%[19,20]. The pharmacokinetics of Δ-9-THC is very fast as its blood concentration decreases of 10% in 2 h. For this reason, blood traces of Δ-9-THC can be detected using standard methods even 4-12 h after *Cannabis sativa* intake[17]. As Δ-9-THC is a highly lipophilic substance, it tends to accumulate in adipose tissue, ready to be released more slowly in other organs, such as the brain. It is estimated that the complete elimination of a single dose may take up to 30 days[21]. The constant assumption of *Cannabis sativa* leads to its gradual accumulation in the body with continuous stimulation of the brain[20,22].

The clinical effects due to use of *Cannabis sativa* can be classified into acute and chronic manifestations[23]. The acute effects include: hyperemesis, motor in coordination, anxiety, tendency to commit acts of suicide and psychotic syndromes (at high doses). For these reasons, the use of *Cannabis sativa* is closely correlated to road and fatal crashes.

The chronic effects linked to *Cannabis sativa* use are: Exacerbation of psychotic reactions in susceptible individuals, withdrawal crisis, neuropsychological deficits, chronic bronchitis in habitual smokers, worsening of angina or provocation of an acute coronary syndrome[16].

Effects of cannabinoids on endothelial function: Atherosclerosis is a major cause of mortality especially in the Western countries[24,25]. Extensive studies indicate that endothelial dysfunction is the "Primum movens" in the pathogenesis and progression of atherosclerosis. A defect in endothelial function is a crucial event in the degeneration of the vascular structures and thus, responsible for the atherosclerotic lesion[26,27]. The role of cannabinoids on endothelial function and therefore, on atherosclerosis is widely reported[28-30].

The first studies on the role of cannabinoids in the cardiovascular system involved urethane-anaesthetized rats[31,32]. These scientific works demonstrated a possible role of CB1 receptors in the inhibition of sympathetic transmission at the presynaptic level on postganglionic sympathetic nerves innervating the heart and vasculature[32]. In fact, the administration of exogenous anandamide causes bradycardia (with secondary hypotension) followed by a sudden and temporary increase in blood pressure and a subsequent drop. A more recent study conducted by Bátkai *et al*.[33] showed the cardiodepressor and vasodilatory action mediated by cannabinoid CB1 receptors. In contrast, the use of CB1 receptor antagonists increased the blood pressure and improved the contractility of the left ventricle in Spontaneously Hypertensive Rats (SHR).

Furthermore, the exposure to anandamide in isolated mesenteric artery and coronary artery of a rat causes vasodilation[34,35,36]. On the basis of these evidences, anandamide has been proposed as an endothelium-dependent vasodilator[34,35,36]. Another study conducted by Deutsch *et al*.[37] confirmed the vasorelaxant role of anandamide in renal afferent arterioles, through endothelium-derived NO. This vasorelaxant effect seems to be blocked by NO synthase inhibition or CB1 receptor antagonism with SR 141716A. The presence of anandamide synthase and amidase enzymes in cultured rat renal endothelial cells seems to suggest that endocannabinoids may be a product of the endothelium. This result seems to be in contrast with the evidence produced by the studies from Randall[34,35,36] which documented an anandamide-mediated vasodilation also

in the absence of the endothelium, revealing a possible action of the endocannabinoid independently from endothelium products.

Plane *et al.*[38] demonstrated the correlation between anandamide, vascular relaxation and increased extracellular concentration of K^+. However, the AEA-mediated relaxation seems to be related to the concentration of extracellular K+ and it is not mediated by activation of CB1 receptors, as it emerged from Randall's studies[34,35,36].

The evidence that the action of AEA is abolished in the presence of a high concentration of extracellular K^+ suggests that cannabinoids may be hyperpolarizing agents. For these reason, Randall *et al.*[3] proposed anandamide as equal to Endothelium Derived Hyperpolarizing Factor (EDHF). In support of this hypothesis, EDHF-mediated vasodilation appears to be inhibited by selective cannabinoid antagonist, SR141716A[34]. Nevertheless, further studies are needed in order to better delineate such a still-debated question.

All these evidences pointed out the juxtaposition of roles of the two cannabinoids receptors because the CB1 receptor agonist promotes atherogenesis, while the CB2 receptor agonist counteracts the onset of atherosclerosis[30]. In particular, CB1 receptors promote the atherosclerotic lesion progress through the activation of Mitogen Activated Protein Kinases (MAPK)[39] and the increased production of Reactive Oxygen Species (ROS)[40]. On the other hand, the selective agonists of CB2 receptors produce: (1) A reduction of the inflammatory response to TNF-α, (2) A decreased expression of vascular adhesion molecules, (3) A decreased endothelial adhesion of monocytes with consequent reduction of their trans-endothelial migration[15,41]. Despite this protective effects carried out by the CB2 receptor against atherosclerosis[42], marijuana smoke has been linked to a worsening of angina pectoris in patients with Coronary Artery Disease (CAD)[43]. The multiple acute effects of marijuana smoking on the cardiovascular system include: Increased heart rate in a dose-dependent way, increased cardiac output, decreased peripheral resistance, increased carboxyhemoglobin with a consequent reduced ability to carry oxygen[44] and a modest increase in blood pressure. Moreover, cases of orthostatic hypotension were reported[45]. These effects are centrally mediated by the autonomic nervous system, while at the peripheral level, are directly determined by the cannabinoid receptors. The tolerance to these hemodynamic changes develops after few doses of marijuana with a consequent gradual reduction of the effects observed in acute setting[46]. Furthermore, marijuana smoke causes less tolerance to physical stress in healthy subjects and an early achievement of maximum heart rate during exercise[47]. Aronow and Cassidy compared the effects of cigarette and marijuana smoke in a population of 10 patients with angina pectoris. They found that the marijuana smoke produces an earlier onset of angina, in terms of both time and effort needed to manifest, as compared to cigarette smoke[48].

Cannabinoids are also related to an increased risk of precipitating an Acute Coronary Syndrome (ACS). In literature, there are cases of acute myocardial infarction after exposure to marijuana smoke in patients without any other risk factors for atherosclerosis[49,50]. The mechanisms related to the cannabinoids-induced myocardial infarction appear to be multifactorial and include: Increased myocardial oxygen demand, decreased blood supply of oxygen, coronary vasoconstriction and platelet activation[20,51]. Mittleman *et al.*[52] reported that the first hour after exposure to marijuana smoke is the time at higher risk for the development of myocardial infarction. The well-established role of cannabinoids on endothelial function encouraged the execution of numerous clinical trials for evaluating their possible therapeutic use. On the basis of pro-atherogenic effect mediated by CB[139,40] the STRADIVARIUS trial (Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant-The Intravascular Ultrasound Study) evaluated the use of Rimonabant, a selective blocker of the CB1 receptor, in the progression of coronary atherosclerosis, assessed by mean of coronary intravascular ultrasound[53]. The results demonstrated a reduction in total volume of atheroma in those undergone Rimonabant administration as compared to controls. This confirmed a role of CB1 receptors in the progression of atherosclerotic lesion. Nevertheless, after 18-month follow-up, the trial failed in demonstrating a reduction in the percent of atheroma volume. Similar results came from the AUDITOR trial (Atherosclerosis Underlying Development Assessd by Intima-Media Thickness in Patients on Rimonabant)[54]. The authors demonstrated the absence of a statistically significant difference between Rimonabant and placebo treated patients in relation to the progression of Carotid Intima-Media Thickness (C-IMT) which is considered an early marker of atherosclerosis and has predictive value for chronic CAD[55,56,57,58,59,60].

The CRESCENDO (Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes) trial was conducted to evaluate the reduction of cardiovascular events in patients treated with

Rimonabant[61]. The trial was stopped prematurely due to the onset of strong suicidal tendencies in patients treated with the selective CB1 receptor blocker. However, during the period of treatment -13.8 months-there were no statistically significant differences between the two groups regarding the occurrence of adverse cardiac events, such as myocardial infarction and stroke[61]. Therefore, the use of a selective blocker of CB1 receptors does not modify significantly the natural evolution of the atherosclerotic lesion.

In contrast, an agonist of the CB2 receptor with anti-atherogenic activity might have a possible role in the modulation of atherosclerosis, although at the moment no evidence exists about it. A study from Netherland *et al*.[62] evaluated the effects of systemic deletion of the gene encoding for CB2 receptors in Low Density Lipoprotein Receptor-deficient (Ldlr(-/-)) mice[62]. The authors demonstrated that the silencing of CB2 receptor results in the progression of the atherosclerotic lesions and in the instability of the vascular plaque[62].

CONCLUSIONS

Endothelial dysfunction is a key event in the progression of atherosclerosis and in the pathogenesis of adverse cardiac events. The identification of a role, although still controversial and unclear, of cannabinoids in the progression/modulation of atherosclerosis puts them at the center of scientific debate.

Further studies are needed in order to define a therapeutic strategy that, through the modulation of cannabinoid receptors, will positively act on endothelial function and therefore, will positively influence the natural history and evolution of atherosclerosis.

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