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Pharmacological Properties of the Plant-Derived Natural products Cannabinoids and Implications for Cardiovascular Health

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Abstract

The global march towards legalization of marijuana consumption is pursued in reason of the supposed harmless properties of this plant. Actually, a wide range of cannabinoids is endogenously produced and interacts with different classes of receptors ubiquitously distributed in the human body. Such endocannabinoid system (ECS) modulates several functions in health and disease. However, studies on synthetic ligands with selective agonist/antagonist activity on specific cannabinoid receptors, have clarified how complex the cannabinoid system is. The whole biological activity of cannabis sativa remains difficult to establish, due to the fact that it is a complex mixture of phytocannabinoids with different or even opposing effects. Δ9-tetrahydrocannabinol is the most represented phytocannabinoid in the marijuana plant and then the most studied compound. It has been widely associated with adverse CV effects in marijuana smokers. Conversely, less is known about the role of other phytocannabinoids. Here, we summarized the current knowledge about the effects of phytocannabinoids in CV disease, mainly focusing on atherosclerosis and myocardial infarction. We critically discussed clinical and experimental evidence linking phytocannabinoids to CV disease, attempting at explaining some controversies and suggesting the direction for future studies.

Keywords

Phytocannabinoid · Δ9-tetrahydrocannabinol · Cannabidiol · Atherosclerosis · Myocardial infarction · Cannabinoid receptor

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17.1 Introduction

Legalization of marijuana consumption for medical and/or recreational use is a global trend that many countries are pursuing in reason of the supposed harmless properties of this plant. However, some cannabis plant breeding exhibits nowadays up to 20% more Δ9-tetrahydrocannabinol (THC) than past decades, without accounting for the large amounts of heavy metals, pesticides and toxins accumulated from the soil. Furthermore, the THC content of synthetic cannabinoids now reaches 200 times that of the cannabis. Altogether, those factors not only justify the alert of health authorities [1, 2] but also represent a flywheel to deepen the pathophysiology of endocannabinoid system. Growing data are linking marijuana consumption with severe cardiovascular (CV) events but conflicting data exist. Such discrepancy may be due to biases in study design, as many variables influence clinical outcome: comorbidities, interactions between phyto- and endocannabinoids and concomitant abuses (e.g. tobacco, alcohol, other drugs). However, maybe more relevant is the discrepancy with experimental findings that are increasingly reporting the beneficial effects of targeting endocannabinoid system on CV health. Developing and testing of synthetic ligand with selective agonist/antagonist activity on specific cannabinoid receptors has contributed to uncover the complex biology of endocannabinoid system and paved the way for the study. Here we will focus on the role of phytocannabinoid in CV disease with particular regard to atherosclerosis and myocardial infarction.

17.2 Endocannabinoids and Atherosclerosis

The atherosclerotic plaque develops as a result of a multi-step process with deep alterations of the anti-thrombotic and anti-adhesive vascular endothelial layer to leading to chronic inflammation facilitating the deposition of altered lipids and inflammatory cells within the sub-endothelial space [3, 4]. Interestingly, atherosclerosis associates with an over-activation of the endocannabinoid system as a result of the altered balance between endocannabinoid synthesizing and degrading enzymes. Several experimental lines suggest that the endocannabinoid signalling plays important roles during the development of an atherosclerotic plaque including regulation of macrophage lipid uptake and recruitment of circulating leukocytes within the vessel wall. As a result, cannabinoids have been proposed as therapeutic targets to modulate vascular inflammation and plaque stability. Oxidized LDLs (OxLDL) are highly atherogenic particles formed in the sub-endothelial space and herein engulfed by monocytes through different scavenger receptors such as CD36 and LOX-1 [5]. Importantly, one of the non-psychoactive cannabis compound called cannabidiol have been reported to inhibit the activity of 15-lipoxygenase [6], the enzyme regulating active lipid oxidation thus potentially reducing plaque burden. This process drives the formation of foam cells releasing high amount of pro-inflammatory cytokines thus fuelling the atherosclerotic process [4]. Oppositely, the reverse cholesterol transport by ABCA1 and ABCG1 allows for the transfer of lipid to the anti-atherogenic HDLs and reduce the amount of lipid droplets within foam cells [7]. OxLDL have been shown to directly modulate endocannabinoid signalling in vitro by increasing 2-AG and AEA levels as well as CB1 and CB2 receptors (CB1 and CB2, respectively) expression in cell lines of mouse monocyte as well as in rat peritoneal macrophages. As a result, monocytes reduce the expression of expression of ABCA1 in RAW264.7 cells and increase that of scavenger receptor CD36 thus leading to increased intracellular cholesterol levels [8]. Interestingly, this effect was reversed by pre-treatment with the CB1 inhibitor AM251 suggesting this receptor as a possible target for anti-atherosclerotic therapies [8]. When overloaded by cholesterol, macrophages undergo necrosis and release DAMPs thus further entraining the vascular pro-inflammatory milieu and facilitating the formation of the necrotic core [4]. Here again, CB2 seem to play a beneficial role in facilitating macrophage apoptosis as opposed to necrosis in response to oxLDL via modulation of

the pro-survival Akt pathway [9]. Cholesterol accumulation impairs apoptotic cell clearance and facilitates inflammasome activation, of interest endocannabinoids have been shown to directly activate the NLRP3-IL1β pathway through CB1 in a mouse model of diabetes mellitus [10]. Although interesting, the extent to which those mechanisms might affect macrophage pathophysiology during atherosclerosis remains to be determined. The experimental role of endocannabinoid signalling in atherosclerosis has been investigated at different stage of the disease: from early endothelial dysfunction to the latest plaque rupture and thrombus formation. Interestingly, interference with the CB1 inverse agonist rimonabant seems to ameliorate endothelial dysfunction in isolated aortic rings of apolipoprotein E knockout ($ApoE^{-/-}$) mice [11]. Accordingly, when treated with AEA or others CB-1 agonists, primary human endothelial cells treatment showed reduced viability and increased ROS production [12]. Those deleterious features were successfully prevented by pre-treatment with CB1 antagonists, underlying an important role for this receptor in the development of vascular endothelial dysfunction [12]. This being said, the effect of CB1 antagonism on experimental atherosclerosis showed important differences between different animal strain with rimonabant successfully reducing plaque growth in the LDL receptor knockout ($Ldlr^{-/-}$) animals but not in $ApoE^{-/-}$ models [11, 13]. On the opposite, the anti-atherogenic role of CB2 have been shown by pharmacological and genetic (i.e. Cnr2−/− mice) models both in $ApoE^{-/-}$ and $Ldlr^{-/-}$ strains [14, 15], although some controversies still exist [16]. In this context, synthetic or plant-derived cannabinoids have shown important anti-inflammatory features by blunting the levels of pro-inflammatory cytokines thus reducing dysfunctional endothelial cell activation and macrophage infiltration [14, 17–19]. Specifically, THC has shown to blunt human T-cells proliferation and to inhibit the release of IFN-gamma thus reducing the formation of pro-inflammatory T-helper 1 lymphocytes [20]. Accordingly, CB2 is expressed at high levels by immune cells where it is supposed to play an anti-inflammatory role [14, 21]. Of interest, the anti-inflammatory and cytostatic properties of CB2 have been confirmed also in preliminary in vitro experiments employing human endothelial and vascular smooth muscle cells thus highlighting the potential translational value of those findings [22, 23]. Together with their receptors, some studies supported the role of endocannabinoids or plant-derived cannabinoids in atherosclerosis. Steffens and colleagues showed a decreased atherosclerotic progression in in murine models of atherosclerosis after oral administration of low-dose THC [17]. Also, they reported the presence of anti-inflammatory CB2 receptor in both human and mouse atherosclerotic plaques. Lymphocyte isolated from THC-treated resulted less active, while macrophage treated with THC in vitro showed blunted chemotaxis, an important process for atherosclerotic plaque growth [17]. Of importance, all these effects were completely reversed by a specific CB2 receptor antagonist underlying once more the important anti-inflammatory function of this receptor [17]. On the opposite, increased AEA signalling by genetic or pharmacological inhibition of its metabolizing enzyme FAAH associated with worsened atherosclerotic plaque development via enhanced CXCL1-mediated neutrophil recruitment as well as impaired vascular repair [24–26]. Less clear is the role of another molecule of the endocannabinoid superfamily, 2-AG. Initial reports using mice with genetic deficiency of its metabolizing enzyme (i.e. MAGL) on a $ApoE^{-/-}$ background suggested an anti-atherogenic role for this molecule through CB2-mediated reduction of lipid and inflammatory plaque content and enhanced collagen deposition and fibrous cap thickness [27]. Further experiments revealed a facilitating effect on the development of early plaques in $ApoE^{-/-}$ animals fed with high-fat diet and treated with the MAGL inhibitor JZL184 [28]. Lastly, another study supported an athero-protective effect of genetic or pharmacological MAGL blockade on atherosclerosis onset via increased CB2 and blunted CB1 signalling [29]. Although apparently controversial, these results might find an explanation in the different efficiency of MAGL inhibition which depends on the selected dose of the inhibitor, the

way and frequency of administration [30, 31]. Recently, the orphan-receptor GPR55 has been suggested to mediate endocannabinoid signalling by binding the endocannabinoid-like compound palmitoylethanolamide (PEA) as well as the endocannabinoids AEA and 2-AG [32, 33]. Interestingly, GPR55 is highly expressed on the surface of human leukocytes, specifically by monocytes and natural killer cells [34]. Here, in vitro data suggested GPR55 to play a role in oxLDL accumulation [34]. Recently, our group tested the potential role of this receptor in the setting of atherosclerosis by treating ApoE$^{-/-}$ mice under both normal chow and high-fat diet with the GPR55 antagonist CID16020046 [35]. Although, treatment with CID16020046 did not affect the plaque size, GPR55 blockade associated with features of plaque destabilization (i.e. increased intraplaque MMP9 and neutrophil content and reduced collagen deposition) only in animals fed with normal chow. Furthermore, we reported treatment with CID16020046 to induce degranulation of human neutrophil in vitro [35]. Hence, GPR55 might negatively regulates neutrophil chemotaxis and activation thus potentially playing a plaque stabilizing role in the setting of atherosclerosis [35]. Again, some of the anti-atherosclerotic effects of plant-derived cannabinoids might be mediated by this receptor as THC have been reported as its active ligand [36]. Lastly, another research group suggested GPR55 as the possible mediator for PEA anti-inflammatory and anti-atherogenic effects in ApoE$^{-/-}$ animals. In this work, treatment with PEA associated with reduced plaque formation and increased plaque stability via down-regulation pro-inflammatory macrophage activation. Mechanistically, PEA increased the expression of the phagocytosis receptor MerTK and enhanced macrophage efferocytosis in vitro, an effect blunted in macrophages obtained from GPR55 knockout animals [37]. In conclusion, cannabinoids might exert opposite pathophysiological roles in atherogenesis due to their actions on the different receptors. Among the endocannabinoid-related signalling pathways, CB1 seems to hold pathophysiological role in atherosclerosis as outlined by both experimental and clinical studies. Interfering with CB1 overactivation in selected patients might effectively reduce atherosclerotic burden directly by reducing vascular inflammation and indirectly through the improvements of metabolic risk factors.

17.3 Cannabinoids and Myocardial Injury

A growing body of evidence associates recreational use of marijuana with a wide range of myocardial injuries ranging from coronary thrombosis and subsequent myocardial infarction (MI), cardiomyopathies, heart failure and arrhythmias, up to sudden death [38]. Marijuana smoking increases the risk of MI up to about five-fold in the first hour after exposition [39]. During long-term follow-up, the risk drops down to 2.5-fold in the less than once for week smokers, whereas it has exacerbated in more frequently smokers [40]. Noteworthy, very long-term follow-up (up to 18 years) in MI survivors did not demonstrate any significant effect of marijuana use on mortality [41]. Nevertheless, a recent French epidemiological study on young consumers reported an increased number of severe CV complications that raised further concerns about the use of marijuana. Dose of marijuana certainly has a major role alongside with frequency of use, route of administration and duration of use. As reported in animal models, detrimental CB_1 receptor (CB1) activation occurs at high dose of THC with the most common effects represented by increase of heart rate and blood pressure lowering. Therefore, the dramatic increase of THC content in cannabis (from 2–3% up to 20%) may largely explain the epidemiological rise of CV complication related to marijuana use [1]. Conversely, very low dose of THC does not elicit substantial CB1 activation but rather acts as CB2 agonist with anti-inflammatory and anti-oxidant effects [17, 42]. Even, a single ultralow dose of THC exerts cardio-protective effect in experimental model of MI [43]. Chronic administration of low-dose THC could also induce a CB1 down-regulation, but data in this field are still controversial and limited to the central nervous system

[44, 45]. Although THC represents the prevalent compound of marijuana many other cannabinoids are contained within the plant. Among them, cannabidiol (CBD) is highly expressed in different varieties of marijuana and strongly differs from THC. CBD has low activity on CB1 and CB2 and preferentially acts as a CB2 inverse antagonist, property that may explain its anti-inflammatory activity [46]. This effect largely explains the cardio-protective role of CBD: a reduced inflammatory cell infiltration characterizes mouse model of MI, whereas no effect of CBD was observed in isolated heart model [47]. CBD activity on inflammatory cells involves bot canonical (CB1 and CB2) and non-canonical receptors, ultimately suppressing immune cell recruitment and activation [48, 49]. With the same mechanisms, beneficial effects of CBD were later demonstrated in animal models of doxorubicin-induced and diabetic cardiomyopathy and myocarditis as well. In addition, direct effects on cardiomyocytes were reported, including the restoring of mitochondrial function with consequent suppression of oxidative stress, NF-κB and cell death program [50–53]. Less important are other cannabinoids and terpenoids contained in the marijuana plant [54] excepted the tetrahydrocannabivarin, a CB2 agonist with a dose-dependent effect on CB1 (antagonist at low and agonist at high dose). Its beneficial effects are still limited to preclinical evidence on metabolic disorders [55].

17.4 Future Perspectives and Conclusion

The involvement of endocannabinoid system in CV health has been clearly widely demonstrated and strong is the claims for developing even more selective compounds. Conversely, clinical indications for the use of phytocannabinoid are still limited to end of life therapies (e.g. chemotherapy-induced nausea, AIDS- and cancer-related cachexia). Even the application for the treatment of pain is still discussed. Promising results are coming from the use of cannabidiol, even in CV disease. Conversely, the role of the other non-THC phytocannabinoid still remains unexplored in the context of CV health. Eventually, limiting or even eliminating THC from cannabis extract would have sense in order to clarify the potential therapeutic role of the other phytocannabinoids. In that case, for any potential future clinical application physicians will have to carefully monitor the development of adverse psychiatric effects.

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