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Cannabinoids for therapeutic use in atherosclerosis[1]

Summary

Atherosclerosis remains the primary cause of heart disease and stroke that causes about 50% of all deaths in Western countries. The identification of promising novel anti-atherosclerotic therapeutics is therefore of great interest and represents a continued challenge to the medical community.

Cannabinoids, such as Δ9-tetrahydrocannabinol (THC), the major psychoactive compound of marijuana, their synthetic analogs and endogenous cannabinoid ligands, produce their biological effects by interacting with specific receptors. In a mouse model of atherosclerosis, we have recently shown that THC inhibits disease progression through pleiotropic effects on inflammatory cells. Blocking of cannabinoid receptor CB_2, the main cannabinoid receptor expressed on immune cells, abolished the observed effects. The potential therapeutic benefit is in conflict with the known health risks of marijuana use, as THC also binds to and activates neuronal CB_1 cannabinoid receptors. Besides its well known neurobehavioral effects, THC also mediates cardiovascular effects such as vasodilation and hypotension. The development of novel cannabinoid receptor ligands that selectively target CB_2 receptors and are devoid of adverse effects might overcome this problem. In addition, pharmacological modulation of the endocannabinoid system might also offer a new therapeutic strategy in the treatment of atherosclerosis. Several reports demonstrating an implication of the endocannabinoid system in different inflammatory conditions support this hypothesis.

Key words: atherosclerosis; chronic inflammation; cannabinoids

Zusammenfassung

Atherosklerose (Arteriosklerose) stellt nach wie vor die Hauptursache für Herzerkrankungen und Schlaganfall dar und ist für etwa 50% aller Todesfälle in der westlichen Gesellschaft verantwortlich. Ein grosses Interesse für die Medizin besteht daher in der Entwicklung neuer anti-atherosklerotischer Therapien.

Cannabinoide, wie zum Beispiel die in Marijuana hauptsächlich enthaltene psychaktive Substanz Δ9-Tetrahydrocannabinol (THC), erzielen ihre biologische Wirkung durch Interaktion mit spezifischen Rezeptoren. Im Mausmodel konnten wir kürzlich zeigen, dass THC das Fortschreiten der Atherosklerose mittels vielseitiger Effekte auf inflammatorische Zellen verlangsamt. Durch Blockierung des vorwiegend auf Immunzellen vorhandenen Cannabinoid-Rezeptors CB_2 wurden all diese Effekte verhindert. Der potentielle therapeutische Nutzen steht im Konflikt mit dem bekannten Gesundheitsrisiko, welches mit dem Konsum von Marijuana verbunden ist. Denn es ist bekannt, dass THC auch an den neuronalen Cannabinoid-Rezeptor CB_1 bindet und somit aktiviert. Neben den bekannten bewusstseinsverändernden Auswirkungen verursacht THC auch kardiovaskuläre Effekte wie Vasodilatation und Hypotension. Die Entwicklung neuer Cannabinoid-Rezeptor-Liganden ohne die ungewünschten Nebenwirkungen könnte helfen, dieses Problem zu überwinden. Zudem könnte die pharmakologische Manipulation des Endocannabinoidsystems eine neue Therapiestrategie zur Behandlung von Atherosklerose darstellen. Verschiedene Studien, welche auf eine Beteiligung des Endocannabinoidsystems in verschiedenen inflammatorischen Situationen hinweisen, unterstützen diese Hypothese.

Schlüsselwörter: Atherosclerosis; chronische Entzündung, Cannabinoide

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Introduction

The discovery of membrane receptors that bind the psychoactive compound of marijuana, Δ9-tetrahydrocannabinol (THC) and their endogenous ligands has led to the description of the endocannabinoid system [1–5]. Within the last years, a whole signaling system has been identified, composed of the two known receptors, endogenous ligands and enzymes for ligand biosynthesis and inactivation [6]. All endocannabinoids identified so far are derivatives of long-chain polyunsaturated fatty acids and exhibit varying selectivity for the two cannabinoid receptors [7]. In the past few years, many different regulatory actions have been attributed to endocannabinoids, and their involvement in several pathophysiological conditions is subject of ongoing investigations. Consequently, the endocannabinoid system represents an attractive target for drug developing pharmaceutical companies.

Cannabinoid receptors

Both cannabinoid receptors are G protein-coupled receptors that modulate second messengers and signaling components such as adenylate cyclase [8], mitogen-activated protein kinases [9] or members of the NF-κB family [10, 11]. The tissue distribution of the two receptors is likely to account for the well-known psychotropic and peripheral effects of THC. Cannabinoid receptor 1 (CB_1) is expressed predominantly in the central and peripheral nervous system, while cannabinoid receptor 2 (CB_2) is present on immune cells [12]. Thus, CB_2 receptors may have physiological importance in immune response, inflammation and chronic pain [13]. So far, the presence and function of CB_2 receptors in central nervous system (CNS) neurons were controversial. However, a recent study demonstrates the expression of functional CB_2 receptors on brainstem neurons [14]. Substantial evidence further suggests the presence of the endocannabinoid system in liver, pancreas and adipocyte tissue, indicating its regulatory role in metabolic functions [15–20]. A recent study demonstrating endocannabinoid signaling in gingival tissue and receptor upregulation in response to inflammatory stimulation further indicates a modulatory function of the endocannabinoid system in periodontal inflammation [21]. In addition, CB_2 receptors have been implicated in bone mass regulation [22–24].

Moreover, there is emerging evidence suggesting that some cannabinoid effects are not mediated by either CB_1 or CB_2 receptors, which implicates additional receptors involved in these actions [25]. These include the transient receptor potential channels of type V_1 ($TRPV_1$), also known as vanilloid VR_1 receptors [26] as well as peroxisome proliferator-activated receptor (PPAR) gamma [27, 28].

The fact that CB_1 and CB_2 are differentially expressed depending on the cell differentiation and activation status may represent a major mechanism by which the endocannabinoid system is involved in immune functions. Indeed, stimuli such as phytohemagglutinin (PHA), lipopolysaccharide (LPS), phorbol myristate acetate (PMA), cytokines or mitogenic antibodies have been reported to regulate the expression of CB_1 and CB_2 [13].

Cannabinoids and immunomodulation

The development of selective agonists, antagonists, and transgenic mice lacking CB_1 and CB_2 receptors has contributed to broaden our current understanding of cannabinoid biology. As a consequence, the capacity of cannabinoids to regulate immune function is now well established. In vitro, THC treatment of human immune cells inhibits secretion of proinflammatory cytokines and chemokines and triggers the differentiation into a Th2 phenotype [29, 30]. As demonstrated, a CB_2-specific antagonist abrogates the majority of these immunomodulatory effects [30]. Moreover, THC-mediated inhibition of T helper cell activation is absent in CB_2-deficient mice, supporting the hypothesis that the immunomodulatory effects of cannabinoids are CB_2-dependent [31].

Cannabidiol, the major non-psychotropic constituent of the Cannabis sativa plant, has been reported to ameliorate chronic inflammation in murine collagen-induced arthritis, a mouse model of rheumatoid arthritis, by inhibiting antigen-specific lymphocyte proliferation and IFN-γ secretion [32]. Several reports described beneficial effects of cannabinoids in experimental animal models of multiple sclerosis. These effects not only affected tonic control of spasticity, but also inflammatory responses in the spinal cord [33, 34]. Interestingly, two studies employing selective inhibitors of endocannabinoid cellular uptake demonstrated improved motor function and diminished inflammatory responses in a mouse model of multiple sclerosis [35, 36]. By preventing the uptake and thus degradation of

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endocannabinoids, the inhibitors enhance their half-life in vivo. In both studies, the authors observed a decreased expression of major histocompability complex (MHC) class II antigen, nitric oxide synthase and proinflammatory cytokine expression.

Effects of THC on atherosclerosis

Encouraged by the vast number of studies demonstrating immunomodulatory properties of cannabinoids, we recently tested the anti-atherosclerotic potential of THC in a murine model [37]. In our study, we used the apolipoprotein E knock out (ApoE$^{-/-}$) mouse model. These mice rapidly develop hypercholesterolemia and atherosclerotic lesions when fed at high cholesterol diet for only a few weeks. We found that THC inhibited progression of established atherosclerotic lesions (fig. 1). This was associated with reduced proliferation and IFN-γ secretion of lymphoid cells as well as reduced macrophage infiltration into atherosclerotic lesions. Moreover, we detected CB_2 receptor expression within human and mouse atherosclerotic lesions (fig. 2). In vitro, we observed that THC inhibited macrophage chemotaxis in response to MCP-1 and reduced expression of the chemokine receptor CCR2. Importantly, these effects were blocked by a specific CB_2 receptor antagonist [38]. It is particularly noteworthy that the observed in vitro and in vivo effects of THC were dose-dependent. The dose dependency showed a U-shaped curve, where both higher and lower doses were inactive. The effective dose was lower than the dose usually associated with psychotropic effects of THC. However, it is difficult to translate our findings obtained in the used apolipoprotein E knockout (ApoE$^{-/-}$) mouse model of atherosclerosis to humans. We found very low nanomolar concentrations in blood serum of THC-treated mice, which might be a consequence of local THC storage within fat tissue, as cannabinoids are known to be very lipophilic. Indeed, several animal experiments have demonstrated that the instant uptake and unlimited storage of THC by neutral fat limits the molecular concentration of the drug present in plasma [39–41]. The hypercholesterolemic ApoE$^{-/-}$ mouse model is characterised by a strong accumulation of fat tissue, especially within the vessel wall. Thus, THC might be stored within atherosclerotic lesions, resulting in high local concentrations at inflammatory sites. Additional experiments are warranted to clarify whether local accumulation of THC contributes to the anti-atherosclerotic effect, and whether similar THC concentrations may be effective in humans.

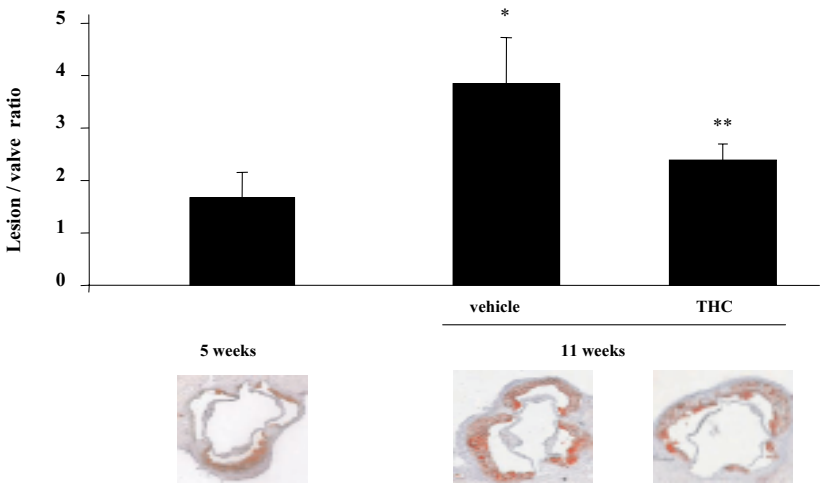

Figure 1
Reduced atherosclerotic plaque development and macrophage content in THC-treated apoE$^{-/-}$ mice. Representative cryosections of mouse aortic roots, stained for lipid deposition by Sudan IV, and quantification of atherosclerotic lesions. After 5 weeks of feeding with a high cholesterol diet, apoE$^{-/-}$ mice developed atherosclerotic lesions (n = 5). THC (1 mg kg^{-1}) was orally administered during the last 6 weeks of the 11 week diet group (n = 6 for THC and n = 8 for controls). Data represent mean values ± SEM.
* p <0.05 vs apoE$^{-/-}$ 5 weeks;
** p <0.05 vs apoE$^{-/-}$ 11 weeks without THC.

Potential role of endocannabinoids in atherosclerosis

Today, it remains unclear whether receptor signaling via endocannabinoids plays a modulatory role in chronic inflammation ongoing during atherogenesis. Several reports demonstrating an implication of the endocannabinoid system in different inflammatory conditions support this hypothesis. For example, a recent study demonstrates that CB_1 receptors mediate intrinsic protective signals that counteract proinflammatory responses in a mouse model of colonic inflammation [42]. A different report provides evidence for the involvement of CB_2 receptor signaling in cutaneous inflammation [43]. Furthermore, endocannabinoid signaling has been implicated in periodontal inflammation, as both cannabinoid receptors CB_1 and CB_2 were upregulated under pathological conditions [21]. Finally, two studies have shown that pharmacological modulation of the endocannabinoid system to increase the half-life of endocannabinoids might have a therapeutic potential for the treatment of multiple sclerosis [35, 36].

To clarify the role of the endocannabinoid system during atherosclerosis, additional

studies employing selective CB_1 and CB_2 receptor antagonists or cannabinoid receptor deficient mice are warranted.

Cardiovascular effects of cannabinoids

Although cannabinoids may be of therapeutic use for the treatment of atherosclerosis, these effects are in conflict with the known adverse effects associated with marijuana consumption. Indeed, the bioactive constituents of the marijuana plant and their synthetic and endogenous analogs cause not only neurobehavioral, but also cardiovascular effects such as vasodilation and hypotension [44–47]. However, targeting the endocannabinoid system may also offer novel therapeutic strategies in the treatment of hypertension [48]. Recently published clinical trial reports to test the effectiveness of the CB_1 receptor blocker rimonabant as an antiobesity drug have shown that it also had a significant effect on lipid parameters and several other cardiovascular risk factors [49, 50].

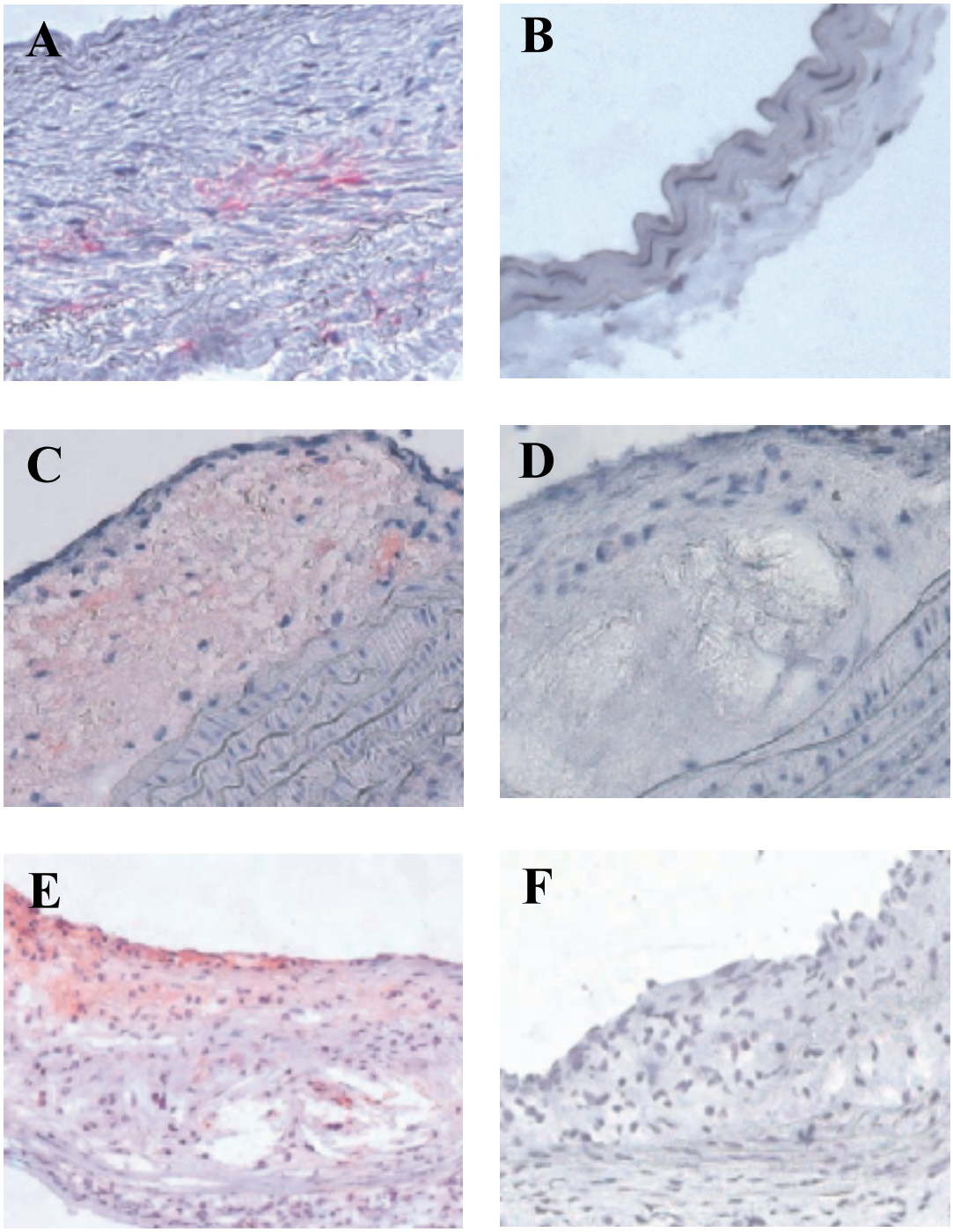

Figure 2
The cannabinoid receptor CB_2 is expressed in human and mouse atherosclerotic plaques. Representative cryosections of human coronary atherosclerotic lesion (A), normal carotid artery from wild-type mouse (B), aortic arch atherosclerotic lesion from $apoE^{-/-}$ mouse (C, D), aortic root atherosclerotic lesion from $apoE^{-/-}$ mouse (E, F). Sections were immunolabeled with an anti-CB_2 receptor antibody (A, B, C, E), or with secondary antibody only (D, F).

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Underlying mechanisms of the cardiovascular cannabinoid actions may involve not only activation of cannabinoid receptors on peripheral nerves, but also signaling via receptors located in the vascular wall [45]. The presence of CB_1 receptors on vascular smooth muscle and endothelial cells as well as experiments performed with isolated arteries provide evidence for this hypothesis [44, 51–53].

Non-psychoactive cannabinoid receptor ligands for therapeutic use

Besides the risk of unwanted cardiovascular effects, a broad acceptance of cannabinoids as therapeutic agents is hampered by the fact that they exhibit psychotropic effects. Therefore, particular research interest is focusing on the development and characterisation of either synthetic or plant derived cannabinoids with therapeutic value that are non-psychotropic [54]. Several non-psychotroptic synthetic cannabinoids with anti-inflammatory properties have recently been developed from plant cannabinoids. Their anti-inflammatory properties suggest that CB_2 ligands may serve as novel immunomodulatory agents in the treatment of immune disorders such as atherosclerosis. However, little is known about the molecular mode of action of these compounds and requires further investigation.

Conclusion

A growing body of evidence suggests a broad therapeutic potential of cannabinoids for a variety of conditions. Nevertheless, the medical use has been very limited in the past, mainly due to the psychotropic effects associated with marijuana use. Now that non-psychoactive cannabinoids become available, it is essential to investigate in more detail the pharmacological and biological activities of these drugs to identify the most powerful and selective agents for therapeutic use. In particular, several newly described synthetic CB_2 ligands with immunomodulatory properties may serve as novel therapeutic agents in the treatment of immune disorders such as atherosclerosis. The recent demonstration that THC mediates anti-atherosclerotic effects in a mouse model via CB_2 receptor-dependent mechanisms suggests that CB_2 activation may attenuate atherosclerosis progression.

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