Cannabinoids and Atherosclerosis

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Abstract: The endocannabinoids are a family of lipid neurotransmitters that engage the same membrane receptors targeted by tetrahydrocannabinol and that mediate retrograde signal from postsynaptic neurons to presynaptic ones. Discovery of endogenous cannabinoids and studies of the physiological functions of the cannabinoid system in the brain and body are producing a number of important findings about the role of membrane lipids and fatty acids. The role of lipid membranes in the cannabinoid system follows from the fact that the source and supply of endogenous cannabinoids are derived from arachidonic acid. The study of molecules which influence the cannabinoid system in the brain and body is crucial in search of medical preparations with the therapeutic effects of the phytocannabinoids without the negative effects on cognitive function attributed to cannabis. Basic information about function and role of the endocannabinoid system is summarized in the paper; possible therapeutic action of cannabinoids, effects on atherosclerosis specially, is described at the close.

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Introduction

Interest in mechanisms of action of cannabinoids is given by their psychotropic but also therapeutic effects. First note about medical use of cannabis comes from China (28th century B.C.) and India (2000–1400 B.C.), later on also from the ancient Egypt, Greece, Rome and Arabic medicine. Cannabis is referred also in medical books of medieval Europe. Detailed historical background to cannabis and cannabis preparation as medicine gives Russo [1]. By the end of the 19th century, cannabis products were widely exploited to treat the pain, whooping cough, asthma and as a soporific or sedation agent. At present, cannabis is listed as an illicit drug without medical use in most countries, although interest in therapeutic use of cannabinoids re-appeared in the mid-1990s.

Tetrahydrocannabinols are responsible for psychotropic properties of cannabis [2, 3] through activation of cannabinoid receptors type 1 (CB_1) in the brain [4]. On periphery, on cells of immune system above all, cannabinoid receptors type 2 (CB_2) are localized. Endogenous metabolites with affinity to cannabinoid receptors were found as far as in the year 1992 [5] and vigorous research followed of the role of endocannabinoid system.

The density of the CB_1 receptors in the brain is comparable to other G protein-coupled receptors, such the Mu opioid receptors and dopamine D2 receptors. CB_1 receptors are numerous in these regions: substantia nigra > globus pallidus > dentate gyrus > hippocampus > cerebral cortex > putamen > caudate > cerebellum > amygdala > thalamus = hypothalamus. Low concentrations were found in brain stem nuclei controlling respiration [6].

CB_2 receptors probably participate in immunosuppressive and antinociceptive effects of cannabinoids [7, 8].

Physiological functions of cannabinoid system are very complex and involve motor coordination, memory, appetite, pain modulation, neuroprotection, and maintenance of homeostasis [9]. Vanilloid/capsaicin receptor (TRPV1) and other subtypes of cannabinoid receptors (non-CB_1, non-CB_2) are involved in these processes. It seems that there is association between obesity and hyperactivity of cannabinoid system.

Endocannabinoids

Endogenous cannabinoids are lipophilic signal molecules, which meet the criteria for listing as neurotransmitters. Unlike classic neurotransmitters they are not synthesized in the cytosol of neuron and they are not stored in synaptic vesicles. They are released from membrane phospholipids by activated lipases and hydrolases in response to membrane depolarization and by an increase of intracellular calcium concentration [10]. *2-arachidonoylglycerol* (2-AG) is the most prevalent endocannabinoid [11, 12], *anandamide* (*N*-arachidonoylethanolamide, AEA) is the most examined endocannabinoid [5]. Noladin ether (2-arachidonoyl glyceryl ether), virodhamine (*O*-arachidonoyl ethanolamine) and *N*-arachidonoyl

dopamine are additional putative endocannabinoids. Endogenous cannabinoids are derived from arachidonic acid, which is one of significant unsaturated fatty acids bound in membrane phospholipids [13]. The role of essential unsaturated fatty acids has been discussed in some biochemical hypotheses of affective disorders, schizophrenia, and neurodegenerative diseases for a long time [13–17]. Endocannabinoids are transported into cell by means of specific transporter or by other, yet unknown mechanism and they are intracellularly metabolised [10, 18]. Anandamide is metabolised by fatty acid amide hydrolase, 2-AG by monoacylglycerol lipase.

Mechanisms of action

Both CB_1 and CB_2 cannabinoid receptors are coupled with $G_{i/o}$ proteins, which inhibit adenylyl cyclase and stimulate mitogen-activated protein kinase [10, 13]. It leads to decrease of cyclic adenosine monophosphate (cAMP) production, inhibition of voltage dependent calcium channels and stimulation of specific potassium channels. Inhibition of calcium ions influx into presynaptic terminals causes reduction of release of different neurotransmitters. Lowered cAMP concentration reduces activation of protein kinase A, which causes lower phosphorylation of voltage-gated potassium channels and further increase of potassium ion efflux. Activation of CB_1 receptors may also affect function of many other receptors which are coupled to G proteins and to activation or inhibition of adenylyl cyclase.

CB_1 receptors come to the most numerous metabotropic receptors in the brain [6]. Inhibition of calcium channels by cannabinoids is able to explain resulting lowered release of different neurotransmitters from presynaptic terminals. This retrograde affection of neurotransmission is evidently the main mechanism of action of cannabinoids in the brain [10] and has significant role in modulation of synaptic plasticity. The main functions of cannabinoid receptors are suppression of GABA release, suppression of release and uptake of glutamate [19, 20] and effect in release of other neurotransmitters [21].

In comparison with opiates, cocaine, alcohol, tobacco or benzodiazepines susceptibility to cannabinoids addiction is relatively low [22, 23] and is given by psychological factors, rather than by physiological. According to present findings, both acute and chronic effects of cannabis abuse are reversible.

Cannabinoid system affect function of series of neurotransmitter systems, whose role is supposed in pathophysiology of schizophrenia, mood disorders, anxiety and neurodegenerative disorders [9, 24–29]. In vulnerable people, cannabis drugs may induce latent schizophrenic psychosis or may unfavourably influence its course, independently of different confounding factors or influence of transient intoxication effect. Available evidence does not strongly support an important causal relation between cannabis use and psychosocial harm, but cannot exclude the possibility that such relation exists [30–32]. The evidence that cannabis use leads to affective or anxious disorders is less strong than for psychosis [33, 34]. Pharmacological

modulation of the endocannabinoid system has been proposed as a novel therapeutic strategy for the treatment of stress-related mood disorders such as anxiety and depression [29].

Therapeutic effects of cannabinoids

A comprehensive overview on the current state of knowledge of the endocannabinoid system as a target of pharmacotherapy was given by Pacher et al. [9]. The favourable effects of cannabinoids on nausea and vomiting, anorexia and cachexia could be regarded as proven. Effects on the spasticity related to sclerosis multiplex or spinal cord injuries, movement disorders (Tourette's syndrome, dystonia, Parkinson's disease, tremor, tardive dyskinesis), asthma and glaucoma are also relatively well-confirmed. Effects on allergies, inflammation, infections, epilepsy, addiction and withdrawal syndromes are less confirmed. In terms of psychiatric syndromes, these involve effects on reactive depression, sleep disorders, anxiety disorders and bipolar disorders. The neuroprotective effects of THC and its effects on autoimmune illnesses, cancer and blood pressure disorders are still being researched [9, 22, 35–38]. Harmful side effects of cannabinoids are not markedly deleterious in indicated cases and at controlled administration, compared to series of commonly used pharmaceuticals (e.g. in treatment of pain and spasticity). Pharmaceuticals containing cannabinoids are available for medical use in some countries, e.g. dronabinol (Marinol®, THC dissolved in sesame oil), nabilone (Cesamet®, synthetic analogue of THC) and Sativex® (a plant-derived cannabinoid extract containing both THC and nonpsychoactive cannabidiol in a 1:1 ratio [39]).

THC derivatives with positive health effects but without psychotropic effects are the current aim of pharmaceutical preparations. Nevertheless also controlled use of phytocannabinoids and their analogues is able to be effective in treatment number of disorders or at elimination of side effects of pharmacotherapy

Cannabinoid system and atherosclerosis

Abuse of cannabis drugs leads to a series of mental and physical changes. While acute effects of cannabis are well-known, knowledge of the influence of chronic cannabis use on cognitive function, neurochemical processes, endocrine and immune systems is not so well-understood. Increasing of static heartbeat, as far as about 60% during first 30 minutes after smoking cannabis, can be dangerous for men with cardiovascular disorder. Effects THC on cardiovascular system are marked and are mediated largely by CB_1 receptors in blood cells and heart. CB_2 receptors are implicated only in preconditioning and ischemia/reperfusion injury of the myocardium. However, new studies demonstrate the existence of novel endothelial and heart receptors (non-CB_1, non-CB_2), which mediate certain cardiovascular effects of cannabinoids [40].

Progression of *atherosclerosis* can be increased by various individual risk factors, as increased concentration of total or low-density lipoprotein (LDL)

cholesterol and triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, hypertension and diabetes. Several possible mechanisms exist for a causative role of *obesity* in atherosclerosis. These include a complex interplay of abnormalities in blood pressure, lipids, glucose, insulin resistance, dysregulated adipokine release, prothrombosis, and inflammation. A number of studies supports hypothesis, that there is close connection between obesity and increased activity of endocannabinoid system [41]. Therefore, *inhibition of cannabinoid CB_1 receptors* belongs to relatively new pharmacological approaches in treatment of obesity and related metabolic state. The inhibition of CB_1 receptors leads to lower food intake, decrease body mass and effects on metabolism (increase of HDL cholesterol concentrations, decrease of triglyceride levels etc.). Rimonabant (Acomplia), the first selective CB_1 antagonist [42], is used in the treatment of obesity and cardiometabolic risk factors involved in obesity. Meanwhile rimonabant has not been authorized by US FDA (Food and Drug Administration) and its usefulness in the treatment of coronary disorders is tested only [43].

There are a number of discrepancies in description of cardiovascular effects of cannabinoids [42]. E.g. the most significant cardiovascular effects of cannabinoids in experimental animals are hypotension and bradycardia. Contrary, in man acute administration of cannabinoids is connected with tachycardia and only chronic administration leads to bradycardia and hypotension. It can be explained by developing of tolerance to the increased heart activity and to changes in blood pressure after frequent abuse of cannabis. This tolerance quickly disappears after drug withdrawal. Endogenous cannabinoids have no distinguished function in cardiovascular regulations under normal conditions, but they are involved in cardiovascular regulation in hypertension when they may hold down elevating of blood pressure through activation of CB_1 receptors [9].

Acute toxicity of THC is low; however, cardiovascular complication connected with abuse of cannabis were described [40, 44]. Cannabinoids may contribute to cardiovascular collapse connected with *myocardial infarction* [9]. It seems that the cannabis can be more frequent cause of myocardial infarction, than was supposed. Recent findings implicate the increased endogenous cannabinoid concentrations in the pathogenesis of hypotension associated with various forms of shock, including hemorrhagic, endotoxic, and cardiogenic shock, as well as the hypotension associated with advanced liver cirrhosis [40]. Contrary, effects of cannabinoids can be linked also to useful effects on cardiovascular system, e.g. they have protective role in progression of *atherosclerosis* and in modulation of *ischemic/reperfusion damage* of brain and myocardium [9, 42, 45]. In addition, it is supposed that the modulation endocannabinoid system can be novel approach in antihypertensive therapy.

So that, although endocannabinoids are included in the protection to ischemic injury, they may contribute to cardiovascular collapse connected with myocardial infarction and circulatory shock [9]. It is hypothesized, that immunosuppressive

effects of THC mediated through CB_2 receptors could be used against atherosclerosis development, because activation of CB_2 receptors is able to decrease infiltration of immune cells to the atherosclerotic plaques. Activation of CB_1 receptors in the brain induces cardiovascular stress response, which increases heart oxygen consumption and lowers blood flow through coronary arteries [46–48]. Endocannabinoids may take also proatherosclerotic effects by induction of platelet activation. Anyway, the precise role of endocannabinoid system in atherosclerosis has not yet been fully recognized.

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