JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2014, 65, 2, 171-181
www.jpp.krakow.pl

Review article

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A NEW FACE OF ENDOCANNABINOIDS IN PHARMACOTHERAPY. PART I: PROTECTIVE ROLE OF ENDOCANNABINOIDS IN HYPERTENSION AND MYOCARDIAL INFARCTION

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Cannabinoids are compounds which were first isolated from the *Cannabis sativa* plant. For thousands of years they have been used for treatment of numerous diseases. Currently, synthetic cannabinoids and endocannabinoids are also known. Cannabinoid receptors, endocannabinoids and the enzymes that catalyze their synthesis and degradation constitute the endocannabinoid system which plays an important role in functioning of the cardiovascular system. The results obtained to date suggest the involvement of endocannabinoids in the pathology of many cardiovascular diseases, including myocardial infarction, hypertension and hypotension associated with hemorrhagic, endotoxic, and cardiogenic shock. Cardioprotective effect and dilation of coronary vessels induced by endocannabinoids deserve special attention. It cannot be excluded now that in the future our better understanding of cannabinoid system will allow to develop new strategies for treatment of cardiovascular diseases.

Key words: *endocannabinoid system, cardiovascular system, arterial blood pressure, heart failure, cardioprotection*

INTRODUCTION

The plant *Cannabis sativa* has been used for centuries for recreational purposes but also for the treatment of medical conditions such as malaria, glaucoma, bronchial asthma, hypertension, constipation, and as an analgesic in labor-related and rheumatic pains. Nowadays preparations obtained from *Cannabis sativa* (marijuana, cannabis, hashish) are the most widely used illegal drugs. The plant *Cannabis sativa* contains about 400 chemical substances, of which 60 have been classified as cannabinoids. The main psychoactive component isolated only in 1964 is Δ^9-tetrahydrocannabinol (THC) (1). Identification of the THC structure initiated chemical synthesis of its analogs in order to establish structural elements responsible for the psychoactive effects. In 1980s it was shown that cannabinoid activity was highly stereoselective which led to the conclusion that it should be mediated by specific receptors. The discovery of cannabinoid receptors in the brain started the search for endogenous ligands of these receptors and changed the initial belief that cannabinoids are substances of exclusively plant origin. In 1992 Devane *et al.* (2) described the isolation of a porcine brain lipid, arachidonoylethanolamide named anandamide (AEA), which mimicked the behavioral actions of THC when injected into rodents and therefore was regarded as an endocannabinoid (EC). A few year latter, Mechoulam *et al.* (3) and Sugiura *et al*. (4) independently identified a second EC, 2-arachidonoylglycerol (2-AG). The discovery of ECs initiated a new era in our understanding of cannabinoid system and the therapeutic usefulness of cannabinoids (natural or synthetic) in the treatment of various pathological conditions.

ENDOCANNABINOID SYSTEM AND ITS COMPONENTS

The endocannabinoid system (ECS) consists of the cannabinoid receptors, the endogenous ligands, anandamide or N-arachidonoyl ethanolamide (AEA) and 2-AG, and their synthetic and metabolic machinery, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) (5) (*Fig. 1*). Two main types of endocannabinoid receptors, CB1 and CB2, have been identified and cloned (6, 7). Also, the existence of a receptor referred to as non-CB1/non-CB2, present in endothelial cells and in the central nervous system (CNS), has been suggested (8). In recent years, three additional "orphan" GPCRs, GPR18, GPR55 and GPR119, have been proposed to be members of the cannabinoid family, although this is still a matter of some controversy (9).

The CB1 receptor exists not only in the CNS but also in the peripheral tissues of the cardiovascular, respiratory, reproductive systems, as well as in the gastrointestinal tract (10).

CB2 receptor occurs mainly in peripheral locations in the cells and organs associated with the immune system and is involved in control of inflammatory reactions (11, 12). Its activation inhibits the release of proinflammatory cytokines and increases the release of anti-inflammatory cytokines (5). However, recent findings suggest that CB2 is also present at low levels in some areas of the brain (13).

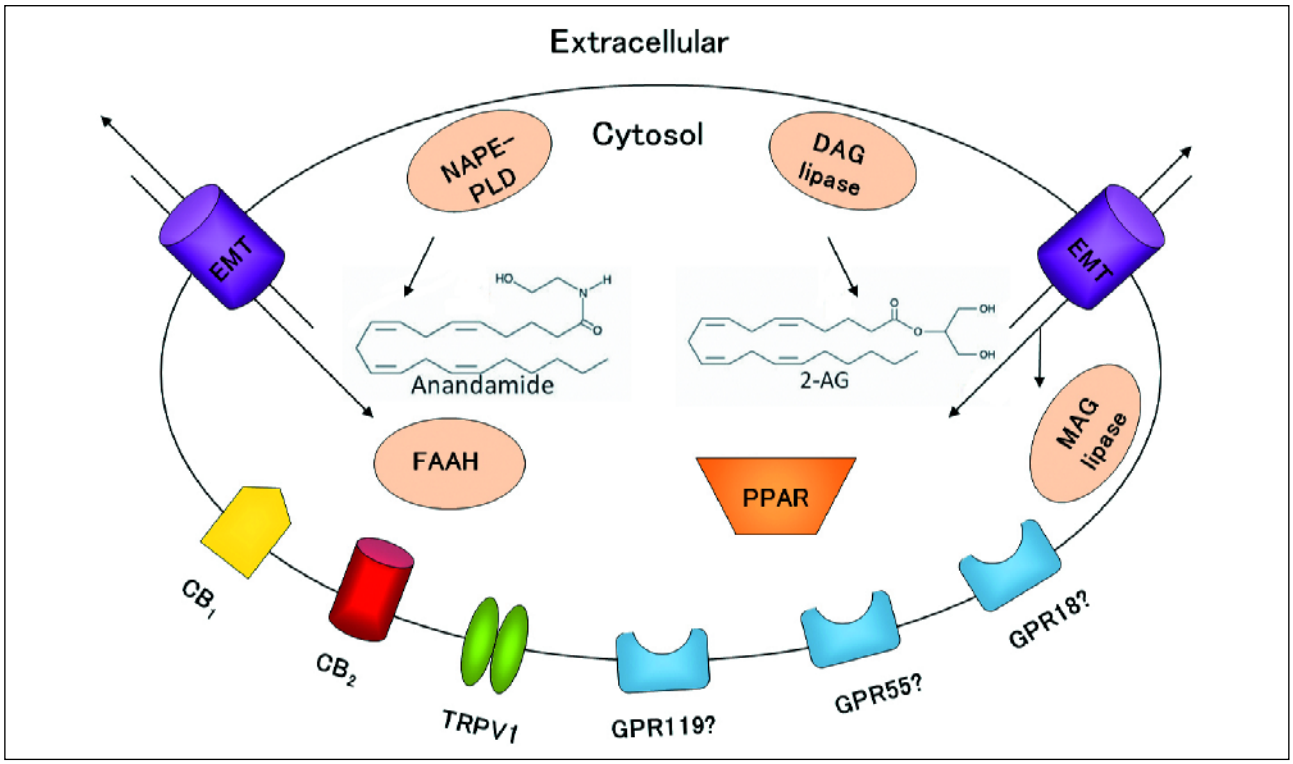

Fig. 1. Elements of the endocannabinoid signalling system. The ECS comprises endogenous compounds such as AEA and 2-AG, their synthesizing enzymes (mainly membrane-bound NAPE-PLD for AEA, and DAG lipase for 2-AG), endocannabinoid membrane transport (EMT) processes, and degradation enzymes (mainly cytosolic FAAH for AEA and membrane-bound MAG lipase for 2-AG) and receptors CB1, CB2, TRPV1 and orphan receptors GPR18, GPR55, GPR119.

As it was mentioned before, two main ECs are AEA and 2-AG. AEA is a partial CB1 receptor agonist, whereas 2-AG is a full CB1 agonist with similar affinity to CB1 and CB2 receptors (14). Two other substances isolated from the brain are presented by some authors as a specific CB2 receptor agonist, palmitoylethanolamide (PEA) (15) and a selective CB1 receptor agonist, oleoylethanolamide (OEA) (16). Their effect is similar to those of cannabinoids. However, because of low affinity to the cannabinoid receptors, they are putative ECs and they cannot strictly be considered a classic ECs although they exert an activating effect on cannabinoid receptors (17, 18), probably acting together with other cannabinoids such as AEA, by inhibiting their inactivation (19). Therefore, they may be regarded as endogenous cannabinoid-like compounds (17, 20). PEA and OEA may be also selective agonists of PPAR (21, 22).

AEA also interacts with several non-cannabinoid receptors, the best characterized of which is the transient receptor potential vanilloid 1 (TRPV1) channel (23), and peroxisome proliferator-activating receptors (PPARs) α and γ (24).

The studies on the role of ECS have become much easier owing to the synthesis of numerous selective cannabinoid receptor agonists and antagonists summarized in *Table 1*.

The ECS constitutes a system of communication between neurons, as well as between neurons and other cells in the CNS and in various peripheral tissues and organs. It is involved in the control of nervous, metabolic, cardiovascular, digestive, reproductive and immune functions, mainly *via* multiple and coordinated local and cell-specific modulatory effects or the release of neurotransmitters, neuropeptides, hormones and cytokines (5). The effect of ECs on the neurotransmission systems results in retrograde inhibition of signal transmission (retrograde antagonism), reduction of the amount of neurotransmitters released from the presynaptic membrane and abolition of neuron activation (5) (*Fig. 2*). The ECS may become deregulated following prolonged perturbations of homeostasis, thus losing its specificity of action and contributing to the progress of several pathological conditions (25).

EFFECT OF ENDOCANNABINOIDS ON CARDIOVASCULAR SYSTEM

The function of the heart is modulated by CB1 and CB2 receptors located pre- and postsynaptically. CB1 receptors are expressed in the myocardium, where they mediate negative inotropy (26-29) and in the coronary and cerebral vasculature where they mediate vasodilation (30, 31).

CB1 receptors are located in the cultured human coronary artery endothelial cells (32) and cardiomyocytes (33), postsynaptically in the blood vessels (34, 35) and presynaptically in the terminals of sympathetic fibers innervating resistance vessels and the heart (36). The excitation of CB1 receptors leads to the inhibition of noradrenaline secretion, and, consequently, to reduced neurogenic pressor response and tachycardia (36).

CB2 receptors are present in the myocardium and cardiomyocytes (29, 33), cardiomyoblasts (31, 37) and in human coronary artery endothelial and smooth muscle cells (38, 39). CB2 signaling in the heart and vasculature may activate cardioprotective mechanisms and limit inflammation (40). Activation of CB2 receptors contributes to ischemic preconditioning and protects against ischemia/reperfusion (I/R) injury in the myocardium (41, 42), as well as in other tissues (38, 43).

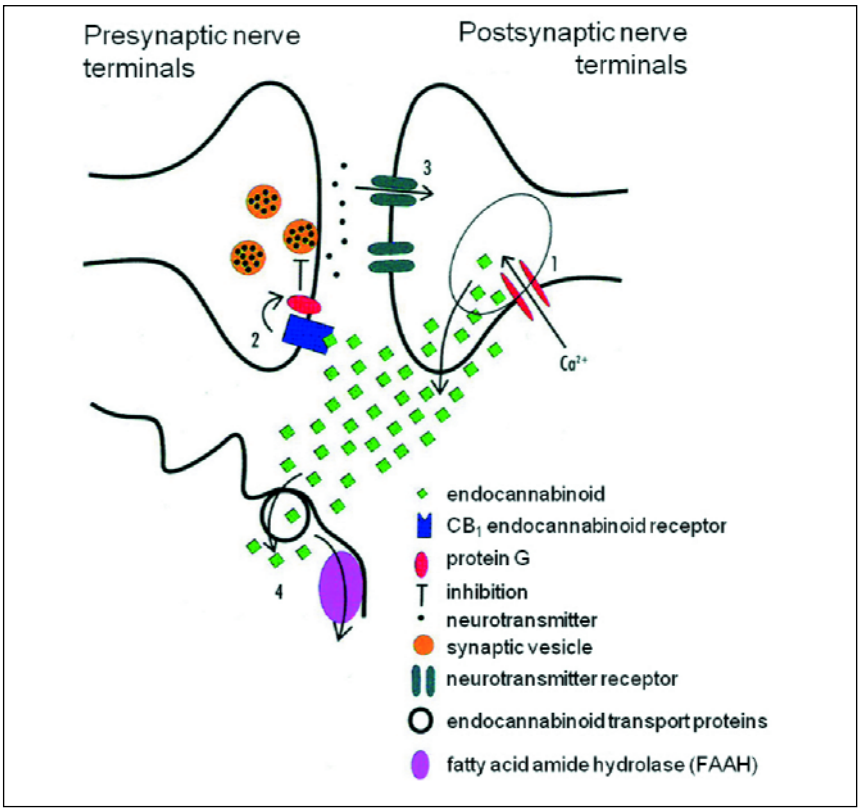

Fig. 2. Retrograde neurotransmitter release inhibition mechanism: 1) the stimulus is followed by depolarization of the postsynaptic membrane and inflow of calcium ions to the neuron; the synthesis of endocannabinoids: AEA and 2-AG is initiated, which are then released into the synaptic cleft; 2) endocannabinoids bind to CB1 on the presynaptic membrane and 3) probably reduce the release of inhibitory neurotransmitters; 4) uptake of unbound endocannabinoids by transport proteins and their degradation by FAAH occurs.

Table 1. Selected natural and synthetic cannabinoids and related substances.

Natural
- **Phytocannabinoids**
  - Δ^9-tetrahydrocannabinol (THC)
  - Δ^8-THC
  - Cannabidiol
  - Cannabigerol
  - Cannabichromene
  - Cannabicyclol
  - Cannabielsoin
  - Cannabitriol

Endogenous
- **Endocannabinoids**
  - N-arachidonoylethanolamide (AEA - anandamide; CB1-CB2 partial agonist)
  - 2-arachidonoylglycerol (2-AG; CB1 complete agonist, CB2 agonist)
  - 2-arachidonoylglyceryl ether (noladin ether; CB1 complete agonist)
  - O-arachidonoyl-ethanolamine (virodhamine; CB2 partial agonist, CB1 antagonist, inverse agonist)
  - N-arachidonoyl-dopamine (CB1 agonist)

Endocannabinoid-related compounds
- Fatty acid derivatives
  - Oleamide
  - Oleoylethanolamide (OEA)
  - 2-oleoylglycerol
  - Stearoylethanolamide
  - Palmitoylethanolamide (PEA)
  - 2-palmitoylglycerol
  - Linoleoylethanolamide
  - 2-linoleoylglycerol
- Archidonoyl-aminoacid

Synthetic
- **Cannabinoid receptor agonists**
  - Classical cannabinoids
    - Delta (8)-THC (CB1-CB2 agonist)
    - HU-210 (CB1-CB2 agonist)
    - O-1184 (CB1 agonist, CB2 inverse agonist)
    - O-1057 (complete CB1-CB2 agonist)
  - Non-classical cannabinoids
    - CP-55 940 (complete CB1-CB2 agonist)
    - JWH-015 (CB2 agonist)
    - L-768242 (CB2 agonist)

Specific CB-1 receptor agonists
- AM-411

Specific CB-2 receptor agonists
- AM-1241
- HU-308
- HU-910
- L-759633
- L-759656
- JWH-015
- JWH-133
- GW405833

Eicosanoids
- WIN-55, 212-2 (complete CB1-CB2 agonist)

Aminoalkylindoles
- methanandamide
- Arachidonoyl-2¢-chloroethylamide
- Arachidonoylcyclopropylamide
- O-1812

2-arylimino-5,6 dihydro-4H-1, 3-thiazines

Arylsulfonamides (CB1 agonists)

Cannabinoid receptor antagonists
- SR141716A (RIO; CB1 antagonist, inverse agonist)
- AM251 (CB1 antagonist, inverse agonist)
- SR147778 (CB1 antagonist, inverse agonist)
- AM281 (CB1 antagonist, inverse agonist)
- SR144528 (CB2 antagonist, inverse agonist)
- LY 320135 (CB1 antagonist)
- AM 630 (CB2 antagonist, partial CB1 agonist)
- LH-21 (CB1 antagonist)

Uptake blockers
- AM 404
- UCM 707
- AM1172
- VDM11
- VDM13
- OMDM1
- OMDM2
- LY 2183240
- LY 2318912
- O-2093

FAAH inhibitors
- OL-135
- URB 597
- URB 532

MAGL inhibitors

JZL 184

URB 602

THE ROLE OF ENDOCANNABINOIDS IN VARIOUS PATHOLOGICAL CONDITIONS RELATED TO CARDIOVASCULAR SYSTEM

Arterial blood pressure

AEA was shown to be involved in the regulation of hypertension. Intravenous AEA injection to rats and mice leads to a characteristic, triphasic response of the cardiovascular system (28, 44). In the first phase, there is an immediate transient decrease in heart rate and cardiac contractility accompanied by a fall in blood pressure known as the Bezold-Jarisch reflex which is mediated *via* vanilloid TRPV1 receptors located on sensory vagal nerves in the heart. In phase II, the AEA-induced brief pressor response and an increase in cardiac contractility depends on both, central and peripheral mechanisms. The central component, involving β-adrenergic and NMDAR receptors, is localized in RVLM and the peripheral one is localized in blood vessels and dependent on calcium ions. In this phase, AEA acts on calcium channels located in the vascular intima and on the specific TRPV1 receptors. In the final phase III, a more prolonged decrease in blood pressure accompanied by a marked decrease in cardiac contractility and a slight decrease in total peripheral resistance occurs. This phase is mediated *via* presynaptic CB1 receptors innervating blood vessels and heart, inhibiting noradrenalin release (45).

Detailed studies demonstrated that only AEA influences the cardiovascular system in such a complex manner. Administration of THC leads to the occurrence of two phases - II and III, whereas treatment with synthetic cannabinoid derivatives (WIN-55.212-2, CP-55.940) causes only long-lasting hypotension and bradycardia (phase III) (46). The vasodilating effect of AEA, leading to hypotension, demonstrated *in vitro,* resulted from stimulation of TRPV1 receptor located on the terminals of sensory fibers supplying the blood vessels (47). The clearest evidence of a role of TRPV1 receptor in the cardiovascular effects of AEA comes from a study using TRPV1 receptor knockout mice (28).

Among other mechanisms mediating vasodilation induced by cannabinoids, the release of nitric oxide (NO) or endothelium-derived hyperpolarizing factor (EDHF) from the vascular endothelium should be mentioned (48, 49). An inhibition of the vasodilating effect of AEA has been observed after damage of coronary arterial endothelium in the ox or pretreatment with an inhibitor of NO synthase (NOS) (50). Mendizabal *et al.* (51) demonstrated that in isolated, perfused mesenteric vascular beds the AEA-induced inhibition of noradrenaline-evoked vasoconstriction was enhanced in rats given NOS inhibitor, L-NAME for 4 weeks. This effect was mediated *via* activation of potassium channels and TRPV1 receptor.

Gardiner *et al.* (52) reported that FAAH inhibition enhanced the cardiovascular actions of AEA. It has been established that preventing the degradation of endogenous AEA by pharmacological inhibition of FAAH reduced blood pressure in hypertensive but not in normotensive rats (27). Thus, modulation of FAAH activity might serve as a useful approach to target EC signaling, especially in areas where there is a significant basal level of endogenous AEA. While little is known about the regulation of FAAH, it is possible that AEA metabolism is altered in hypertensive states and thus contributes to the differential hemodynamic responses in normotensive versus hypertensive conditions (53). In experiments on FAAH knockout mice (FAAH$^{-/-}$), Pacher *et al.* (54) demonstrate that they exhibit increased sensitivity to the CB1-mediated hypotensive and cardiodepressant effects of AEA, and the decreased degradation of AEA rather than altered target organ sensitivity appears to be the underlying mechanism. Furthermore, FAAH –/– mice are reported to have normal blood pressure, cardiac function, and baroreflex sensitivity, and show no evidence of an endocannabinergic tone affecting blood pressure and cardiac contractility.

It has been hypothesized that higher incidence of hypertension and coronary heart disease in males and postmenopausal females may be, at least partially, associated with the vasorelaxant effect of AEA, because estrogen stimulated AEA release from human endothelial cells and the vasodilating effect of AEA was more pronounced in the isolated mesenteric arteries collected from female than from male rats (55). Recent studies suggest that EC signaling is modulated by gonadal hormone 17β-estradiol (17Eβ), however, it is unclear if this applies to the cardiovascular actions of AEA. Studies of the *in vitro* effects of 17Eβ on vasorelaxation to AEA in myograph-mounted small mesenteric arteries obtained from normal and spontaneously hypertensive rats of both sexes demonstrated that pharmacological levels of 17Eβ potentiate mesenteric relaxation to AEA through mechanisms dependent on TRPV1 receptors (56).

In conclusion, among the numerous pathways through which AEA exerts its vasorelaxant effect, the following pathways can be mentioned: activation of the CB1, CB2, non-CB1/CB2, TRPV1, and modulation of ion channel, NO release, metabolism of vasoactive arachidonic metabolites or endothelium-derived hyperpolarizing factor (EDHF) release.

Myocardial infarction

ECs can modulate both acute and chronic cardiac disorders. In the acute phase of myocardial infarction (MI) ECs contribute to the reduction of myocardial necrosis and risk of arrhythmia, while in the chronic phase they are involved in the process of heart remodeling (57, 58). The cardioprotective effect of ECs during myocardial infarction may result from their direct effect on the vascular endothelium or intima, and in coronary diseases also through CB1/CB2 receptor-dependent mechanism (59, 60). ECs have been proposed to protect against myocardial ischemia/reperfusion injury and to contribute to the ischemic preconditioning effect of endotoxin, heat stress or brief periods of ischemia (41, 61, 62). In addition, CB2 receptors have been involved in the cardioprotective effects of remote ischemic preconditioning which is a protective phenomenon induced by preceding ischemia in other organs or vascular beds (59).

Administration of a potent CB2 receptor agonist and experiments carried out on knockout mice have provided compelling evidence that CB2 activation plays a protective role against myocardial I/R by decreasing the endothelial cell activation/inflammatory response (for example, expression of adhesion molecules, secretion of chemokines) and by attenuating leukocyte chemotaxis, rolling, adhesion to endothelium, activation and transendothelial migration, and interrelated oxidative/nitrosative damage (42) (*Fig. 3*). It is therefore plausible that the protective effect of cannabinoids is, at least in part, related to their anti-inflammatory properties mediated by CB2 receptor. Reperfusion strategies are required to resuscitate the ischemic myocardium. Unfortunately, reperfusion itself inflicts additional tissue damage mediated by reactive oxygen and nitrogen species, and inflammation (63, 64) *(Fig. 4).*

Recently, it has been shown that intravenously injected AEA would enhance expression of heat shock protein 72 (HSP72) in the heart and thus render cardioprotection against ischemia/reperfusion injury in rats. The enhancement of HSP72 by AEA was blocked by CB2 but not CB1 antagonist (61).

A significant cardioprotective effect of ECs was also demonstrated on the isolated rat heart model of low-flow induced ischemia/reperfusion injury. The infusion of 2-AG or PEA

reduced myocardial infarct size and prevented the release of LDH and creatine kinase (65, 66). Pretreatment with the CB2 antagonist SR 144528 abrogated the cardioprotective effect of both, PEA and 2-AG, whereas a partial inhibitory effect on 2-AG-mediated activity was observed when the CB1 antagonist, RIO, was used (65). Recently, it has been shown that, CB2-selective agonist HU-308, significantly decreased the infarct size, the levels of ROS and tumor necrosis factor-α (TNF-α) in the presence of AEA and 2-AG in acute myocardial infarction/ischemia/reperfusion model in animals (67). Additionally, it reduces blood pressure and exerts an anti-inflammatory effect (68). Also HU-910, a potent selective CB2 receptor agonist, exerts a protective effect, attenuating oxidative stress and inflammation associated with ischemia/reperfusion tissue injury (69).

Lagneux and Lamontagne (70) were among the first researchers to confirm the beneficial cardioprotective role of ECs in myocardial infarction. They demonstrated that in the isolated hearts of the rats with induced septic shock subjected to 90-minute ischemia, the area affected by necrosis was reduced and the function of left ventricle was improved. The beneficial effect of lipopolysacharide (LPS) was blocked by a CB2 receptor antagonist, SR 144528, but not by a CB1 receptor antagonist, RIO, administered 5 min prior to induction of experimental MI. It was suggested that LPS increases EC production in inflammatory cells, which was attributed to a relationship between cannabinoids and NO.

Analogical results were obtained in experiments involving the exposure of rats to short-term heat stress, which led to reduction of the necrotic area in isolated hearts subjected to I/R injury. Also in that case, the cardioprotective effect of heat stress was blocked by CB2 but not CB1 antagonists (71).

The beneficial effect of CB2 activation on myocardial infarction in mice was recently confirmed in models of ischemia and reperfusion *in vivo* (72, 73). These studies showed that selective activation of the CB2 receptors a few minutes before reperfusion markedly improves MI. The protein kinase C and MAPK pathways can also be involved in the cardioprotective effect of cannabinoids mediated by CB2 receptors. The protective effect of PEA on the heart was markedly attenuated in the presence of p38/ERK1/2 and protein kinase C inhibitors (65). *In vivo*, a beneficial increase of ERK1/2 levels was confirmed by treating mice with the synthetic selective CB2 agonist, JWH-133 (73).

The cardioprotective effect of cannabinoids may be also associated with their influence on leukocyte migration. Experiments carried out on mice indicated that a nonselective cannabinoid agonist, WIN 55.212-2, administered 30 min prior to induction of myocardial ischemia demonstrated a cardioprotective effect dependent on CB2 receptors, reducing the myocardium area affected by infarction by up to 52%. It was also observed that activation of CB2 receptors reduced the number of leukocytes migrating to the ischemic area, while a CB2 antagonist, AM 630, reversed this effect confirming the cardioprotective effect of ECs (74). CB2 activation also decreases ROS production and neutrophil infiltration within infarcted ventricles *in vivo* and *in vitro* (73).

It should also be added that natural and synthetic cannabinoids are effective in modulating pain (75). Down-regulation of the host inflammatory response by inhibiting the release of proinflammatory cytokine plays a putative role in MI pain.

Cardioprotective effect of nitroglycerin was also shown to be mediated by CB1 receptors (66, 76). By contrast, in isolated

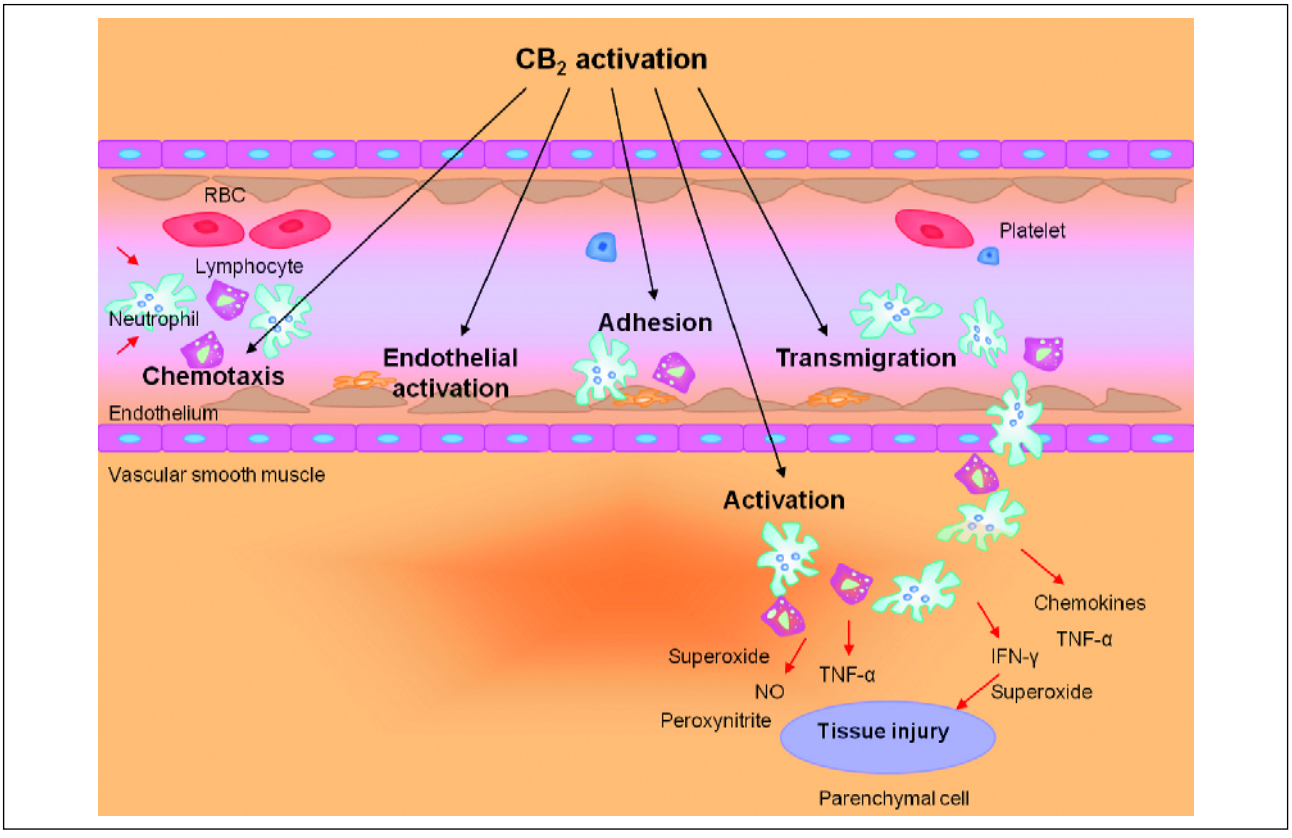

Fig. 3. Mechanisms of CB2 receptor-dependent protection in ischemia/reperfusion (I/R). CB2 receptor stimulation may protect against I/R injury by attenuating endothelial cell activation/inflammatory response, chemotaxis, transmigration, adhesion, and ROS generation.

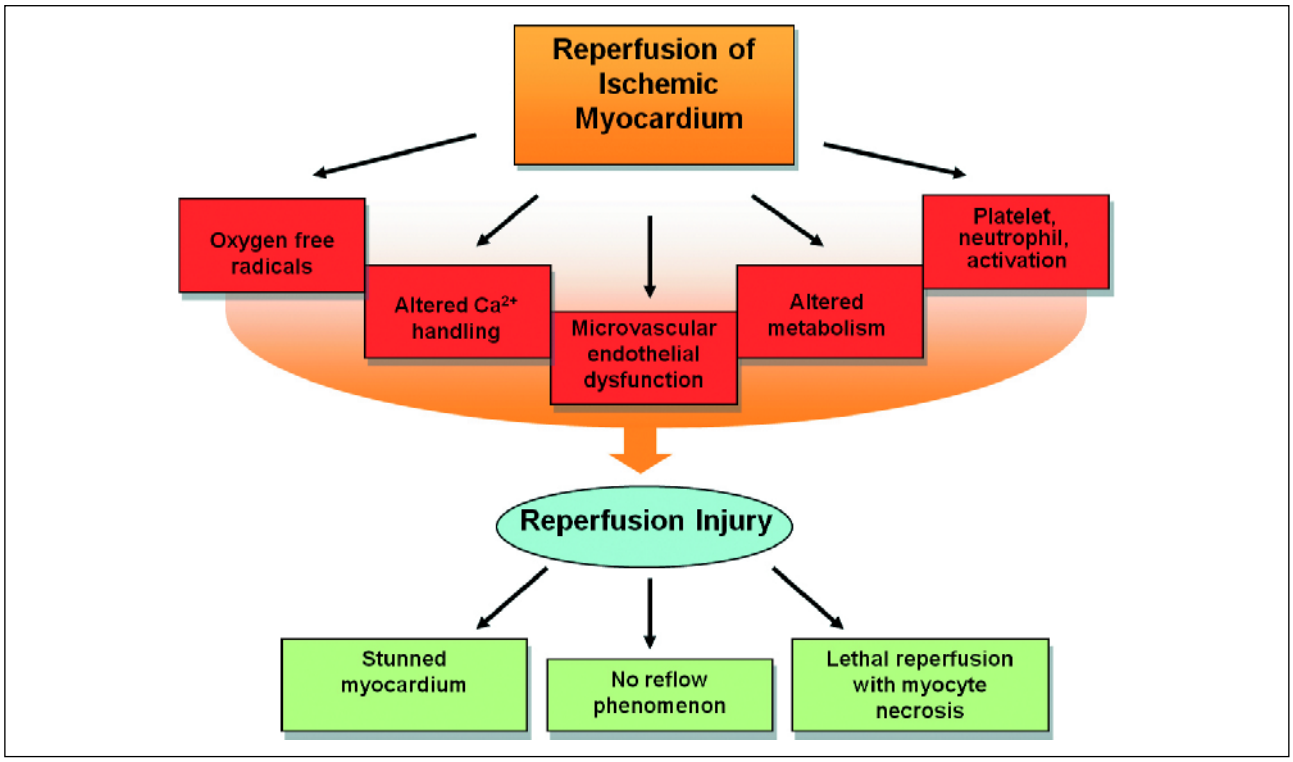

Fig. 4. Mediators in myocardial reperfusion injury. Reperfusion injury results from several complex and interdependent mechanisms that involve the production of ROS, alterations in intracellular calcium handling, microvascular and endothelial cell dysfunction, altered myocardial metabolism, and activation of neutrophils and platelets. Reperfusion injury is manifested as stunned myocardium, reversible microvascular injury, and lethal myocyte necrosis.

neonatal cardiomyocytes preventive effect of the THC against hypoxia was dependent on NO production and mediated by CB2, but not CB1 receptor (37). A single ultra low dose of THC is a safe and effective treatment that reduces MI damage (77).

Arrhythmia

ECs have been shown to reduce the risk of arrhythmia, a common complication of myocardial infarction, through a mechanism mediated by CB2 but not CB1 receptors (59, 78, 79, 80).

In an ischemic-induced arrhythmia model, AEA showed significant anti-arrhythmic effect. During the ischemic period, 76% and 46% of the control animals had multiple ventricular premature beats (VPBs) and ventricular fibrillation (VF), respectively. After AEA treatment, only 21% and 7% of animals developed VPBs and VF, respectively. Similar reduction in arrhythmic events was observed after reperfusion (79). The antiarrhythmic effect of AEA and its stable analog, Met-AEA, was demonstrated to be abolished by SR 144528, a CB2 receptor blocker, but not by RIO, an antagonist of CB1 receptor (80). In another model, the synthetic agonist, HU-210, was able to reduce ischemic-induced VF and ventricular tachycardia (VT) events by up to 90%, through activation of CB2 receptor (78). The antiarrhythmic effect of HU-210 was also demonstrated on arrhythmia induced by epinephrine and aconitine (81-83). Unlike the ischemic model, the antiarrhythmic effect of AEA in epinephrine-induced arrhythmia was not abolished by CB2 receptor antagonist (83).

It was also established that ECs are involved in the cardioprotective phenomenon of "remote preconditioning", induced by mesenteric artery occlusion and reperfusion. In the rat heart this effect was blocked by the CB2 receptor antagonist AM 630 (59).

In all the aforementioned studies it was demonstrated that the antiarrhythmic effect of cannabinoids is mediated by CB2 receptors, whereas the involvement of CB1 receptors in the mechanisms preventing arrhythmias was excluded (59, 79, 80).

The effects of CBD on the onset and evolution of cardiac arrhythmias in injured rat myocardium were also investigated and its administration during ischemia markedly reduced the number of ischemia-related arrhythmias (84). This effect might be related to direct activity on cardiac current and potassium channels (85).

Remodeling after myocardial infarction

Activation of neurohumoral systems plays an important role in post-MI cardiac remodeling (86, 87) and the development of congestive heart failure (88). Remodeling is indicated by an increase in left ventricular operating volume and a rightward shift of passive left ventricular pressure (volume curves with increasing infarct size) (88). ECs share many properties of neurohumoral mediators and it was hypothesized that they may contribute to post-MI remodeling (89).

There are a few studies concerning the role of ECs in the remodeling process. ECS, in addition to its role during the first hours after the infarction, is also active in the process of postinfarction myocardial remodeling (57, 58, 72, 90).

Hiley and Ford (90) demonstrated that chronic, (12-week) treatment with CB1 receptor antagonist, AM 251, first administered 24 hours after induction of a large MI in rats, had caused no change in the expression of CB1 receptors, but accelerated postinfarction left ventricular remodeling and deteriorated myocardial function. However, in contrast to RIO which administered once before ligation of the coronary artery increased the mortality of rats (91), no such effect was observed

in the case of chronic administration of another CB1 receptor blocker, AM 251. On the other hand, treatment with a synthetic nonselective cannabinoid receptor agonist, HU-210 for 12 weeks after ligation of the left coronary artery improved the hemodynamic parameters of heart function in rats, prevented hypotension and decreased the total peripheral resistance index. In was observed only in the cases in which the necrotic area did not exceed 40% of the left ventricular area, which may suggest a favorable effect of cannabinoids only in MI of small extent. However, inhibition of CB1 receptor activity led to deterioration, and their activation to improvement, in systolic function of the heart also in rats with MI affecting more than 40% of left ventricular volume. At the same time, activation of these receptors adversely affected the increase of the late-systolic pressure in the left ventricle of the heart. Defer *et al.* (72) provided substantial evidence for a protective role of CB2 receptors in ischemic cardiac myocyte cell death, fibrosis and cardiac dysfunction. Hearts of CB2 receptor knockout mice had larger infarcts in comparison with wild-type mice and more sustained cell loss 3 days after ischemia, together with accelerated injury and apoptosis in the non-ischemic remote myocardium. Furthermore, increased infiltration of macrophages was observed in the infarct-surrounding myocardium of such mice. Accelerated cardiac remodeling in post-ischemic hearts was documented by higher number of spindle-shaped a-smooth muscle actin-positive myofibroblasts. *In vitro*, cardiomyocytes and fibroblasts were more susceptible to oxidative stress-induced cell death. Long-term effects of cardiac remodeling in the hearts of CB2 receptor knockout mice involved marked fibrosis, accelerated cardiomyocyte hypertrophy, dilative cardiomyopathy and cardiac dysfunction, as reported 4 weeks post infarction. By contrast, wild-type post-ischaemic hearts developed moderate fibrosis and cardiomyocyte hypertrophy, while cardiac function was preserved.

It has been considered for some time that cannabinoid receptors have the potential to regulate apoptosis since they can signal through both pro- and anti-apoptotic pathways (75). Their lipophilicity also means that they have the capability to penetrate cells and act intracellularly, even without the assistance of a membrane transporter. Recently, it has been shown that a number of cannabinoid agents, including HU-210, THC, and AEA, decrease rat heart mitochondrial O_2 consumption (93) and that mitochondria are involved in marijuana-induced cell death (94). Furthermore, vanilloid receptor agonists, which overlap with ECs at least in the form of AEA and OEA, have pro-apoptotic actions on mitochondria (95). These data, together with the observations on apoptosis in FAAH-deprived mice (96), indicate that endogenously produced cannabinoids have strong potential for the regulation of apoptosis, and hence remodeling, in the heart.

Recently, it has been observed that CB1 receptor deficiency promotes cardiac remodeling induced by pressure overload in mice. CB1 inactivation has been demonstrated to promote cardiac remodeling by enhancing the activity of the epidermal growth factor receptor (EGFR) and mitogen-activated protein kinases (p38 and ERK) (57). ECS is known to play a role in regulating myocardial contractility, but the influence of CB1 receptor deficiency on chronic heart failure remains unclear.

DETRIMENTAL EFFECTS OF ENDOCANNABINOIDS IN THE CARDIOVASCULAR SYSTEM IN HUMANS

The presented paper focuses mainly on the cardiovascular system and the beneficial effects of ECs on its physiology and pathology, demonstrated by earlier studies in this area. Rodent models used in the first phase of the research tended to show more positive effects of ECs, not always consistent with the results of corresponding trials in human subjects. However, numerous preclinical studies as well as recent clinical ones suggest that in humans they may have some detrimental effects as well. The recent review by Pacher and Kunos (97) discusses the findings concerning the role of ECs and the potential use of CB1/CB2 receptor ligands in a broader scope, including numerous body systems and their disorders. As far as the cardiovascular system is concerned, negative influence of CB1 receptor signaling has been reported, *e.g.* elevation of resting heart rate in chronic marijuana users (98) hypotensive and tachycardic effect of THC (99), increased heart rate variability in cannabis users (100), increased risk of acute coronary syndrome and infarction in young healthy cannabis users without any previous cardiovascular disease (101, 102).

A more recent study evaluated the consequences of marijuana use and long-term mortality among survivors of acute myocardial infarction, and found that habitual marijuana use among acute infarction patients was associated with an apparent increase in mortality rate (29% higher) over the subsequent 18 years, although this did not reach statistical significance because of the limited sample size (103). Indeed, in a recent case series in healthy children, myocardial infarction was precipitated by synthetic cannabinoid use (104), and another study reported tachycardia, loss of consciousness and diffuse pain in adolescents (105).

Some authors also report unfavorable effects, both cardiovascular and metabolic, of surinabant, a selective CB1 antagonist (106). On the other hand, CB2 signaling is associated with cardioprotective and anti-inflammatory effects (40). Other studies report the involvement of endocannabinoids in a number of physiological functions, *e.g.* their beneficial effect on CB1 receptors in the gastrointestinal tract and in stress-induced gastric ulcers (107). Also the activity of COX, LOX and CYP-450 metabolites of endocannabinoids plays a role in effects mediated in CB receptor-independent mechanisms, *e.g.* inhibitory gastric motor and cardiovascular effects of systemically administered THC depending on hindbrain and peripheral activation of COX (97, 108).

In view of these findings, some of which indicate that in certain cases therapeutic modulation of the ECs systems may promote disease progression, adverse metabolic reactions and inflammation, it should be concluded that this area, although promising, needs careful consideration of interspecies variations and further research aimed at elucidation of the complex mechanisms associated with the activity of these substances in animals and in humans.

CONCLUSIONS

Pharmacological modification of the cannabinoid system function represents a considerable therapeutic potential. It can be expected that obtaining cannabinoid ligands retaining their medicinal properties but devoid of adverse psychoactivity characteristic of THC, will result in the great progress in treatment of diseases in which the efficacy of conventional therapies is limited.

Another promising direction of research can be associated with the compounds inhibiting the process of inactivation of ECs, *i.e.* AEA transporter inhibitors and FAAH inhibitors. Their effect is limited to the areas affected by pathologic processes, which makes it possible to avoid adverse effects associated with systemic activation of cannabinoid receptors.

Abbreviations: 2-AG: 2-arachidonoylglycerol; AEA: anandamide or N-arachidonoyl ethanolamide; CB1: cannabinoid

receptor type 1; CB2: cannabinoid receptor type 2; CBD: cannabidiol; CNS: central nervous system; COX: cyclooxygenase; CYP-450: cytochrome P-450; ECs: endocannabinoids; ECS: endocannabinoid system; EDHF: endothelium-derived hyperpolarizing factor; FAAH: fatty acid amide hydrolase; GPCR: G-protein coupled receptor; I/R: ischemia/reperfusion; L-NAME: nitric oxide synthase inhibitor; LOX: lipooxygenase; LPS: lipopolysaccharide; MAGL: monoacyl glycerol lipase MAPK: mitogen-activated protein kinases; MI: myocardial infarction; NOS: nitric oxide synthase; OEA: oleoylethanolamide; PEA: palmitoylethanolamide; PPARα: peroxisome proliferator-activated receptor α; RIO: rimonabant (SR141716A); ROS: reactive oxygen species; RVLM: ventolateral medulla; THC: Δ^9-tetrahydrocannabinol; TNF-α: tumor necrosis factor-α; TRPV1: transient receptor potential vanilloid 1 channel;

Conflict of interest: none declared.

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Received: July 25, 2013
Accepted: December 16, 2013

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