BBA - Molecular Cell Research 1867 (2020) 118462

Contents lists available at ScienceDirect

BBA - Molecular Cell Research

journal homepage: www.elsevier.com/locate/bbamcr

Cannabinoid-sensitive receptors in cardiac physiology and ischaemia☆

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ARTICLE INFO

Keywords:
CB1
CB2
GPR55
Cannabinoids
Marijuana
Myocardial infarction
Ischaemia/reperfusion

ABSTRACT

The classical cannabinoid receptors CB1 and CB2 as well as the cannabinoid-sensitive receptor GPR55 are widely distributed throughout the mammalian body. In the cardiovascular field, CB1 and CB2 crucially impact on diseases characterized by inflammatory processes, such as atherosclerosis and acute myocardial infarction. Both receptors and their endogenous ligands anandamide and 2-arachidonoylglycerol are up-regulated in the ischaemic heart in humans and animal models. Pharmacological and genetic interventions with CB1 and CB2 vitally affect acute ischaemia-induced cardiac inflammation. Herein, CB1 rather aggravates the inflammatory response whereas CB2 mitigates inflammation via directly affecting immune cell attraction, macrophage polarization and lymphocyte clusters in the pericardial adipose tissue. Furthermore, cannabinoids and their receptors affect numerous cardiac risk factors. In this context, cannabis consumption is debated to trigger arrhythmias and even myocardial infarction. Moreover, CB1 activation is linked to impaired lipid and glucose metabolism and therefore obesity and diabetes, while its antagonism leads to the reduction of plasma triglycerides, low-density lipoprotein cholesterol, leptin, insulin and glucose. On the other hand, activation of cannabinoid-sensitive receptors can also counteract unfavourable predictors for cardiovascular diseases. In particular, hypertension can be mitigated via CB1 agonism and impaired adrenoceptor responsiveness prevented by functional GPR55.

Taken together, current insights identify the cannabinoid system as promising target not only to therapeutically interfere with the vasculature, but also to affect the heart as target organ. This review discusses current knowledge regarding a direct cardiac role of the cannabinoid system and points out its feasible therapeutic manipulation in the ischaemic myocardium.

1. Introduction

Due to analgesic, calming, appetite triggering and supposedly harmless properties of marijuana, a rising number of states and countries legalized its medical and/or recreational consumption. This is contrasted by an increasing number of diverse illegally available synthetic cannabinoids with multiple-fold augmented cannabinoid receptor binding efficiency, exerting devastating health effects [1]. In addition, some cannabis plant breeding exhibit nowadays a horrendously increased Δ9-tetrahydrocannabinol (THC) potency compared to plants grown in former decades [2]. This might account for harmful effects correlated with cannabis consumption. According to the European Drug Report 2017, in the European Union 23.5 million citizens were documented as consumers in 2017 [3]. Consequently, it is mandatory to elucidate the mode of action of the cannabinoid system under physiological and pathological conditions. Acute and chronic marijuana consumption has been linked to severe cardiovascular events such as myocardial and cerebral infarction, arrhythmias, cardiac arrest and death, as reported by various clinical studies and poison centres [2,4]. However, clinical long-term surveys claim the evidence for marijuana-

Abbreviations: 2-AG, 2-arachidonoylglycerol; abnCBD, abnormal cannabidiol; AEA, anandamide; AMI, acute myocardial infarction; AMPK, AMP-activated protein kinase; Ca^{2+}, calcium; cAMP, cyclic adenosine monophosphate; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; CICR, calcium-induced calcium release; CNS, central nervous system; DAG, diacylglycerol; DAGL, DAG lipase; eCB, endocannabinoid; ECS, endocannabinoid system; ERK, extracellular regulated kinase; FAAH, fatty acid amide hydrolase; GPCR, G-protein coupled receptor; I/R, ischaemia/reperfusion; IP3, inositol-1,4,5-triphosphate; KO, knock-out; LDH, lactate dehydrogenase; LPC, lysophosphatidylinositol; LPI, lysophosphatidylcholine; LV, left ventricle, left ventricular; MAGL, monoacylglycerol lipase; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; NAPE, N-acyl-phosphatidylethanolamine; NO, nitric oxide; OEA, oleoylethanolamide; PEA, palmitoylethanolamide; PKC, protein kinase C; PLD, phospholipase D; RNS, reactive nitrogen species; ROS, reactive oxygen species; TGFβ, transforming growth factor β; TNFα, tumor necrosis factor α

☆ This article is part of a Special Issue entitled: Cardiomyocyte biology: new pathways of differentiation and regeneration edited by Marijke Brink, Marcus C. Schaub, and Christian Zuppinger.

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https://doi.org/10.1016/j.bbamcr.2019.03.009
Received 28 November 2018; Received in revised form 4 March 2019; Accepted 15 March 2019
Available online 16 March 2019
0167-4889/

triggered increased risk for acute myocardial infarction (AMI) as limited and neither support nor deny such an association [5].

Conflicting observations most likely originate from inclusion and exclusion criterions of clinical studies and meta-analyses investigating the correlation between cannabis and risk for cardiovascular diseases. When assessing validity of such analyses, a myriad of variables should be considered: interaction of phyto- and endocannabinoids in cannabis users, incomplete health records, existing (cardiovascular drug) treatments, concurrent abuse of tobacco, alcohol and other drugs such as cocaine, and disproportionate rates of comorbidities. Besides, active cannabis ingredients are complicated to be dosed especially when inhaled.

Basic research meanwhile identified targeted interventions with the endocannabinoid system (ECS) as promising therapeutic approaches to mitigate cardiovascular disease progression. Contradicting results between poison-centre observations and basic research may at least in part be explained by global ECS stimulation in marijuana smokers on the one hand and partial targeting of cannabinoid receptors in pharmacologically and genetically manipulated animal models on the other hand. The route of administration of ECS stimulating agents may also account for the divergent observations.

By now, various experimental and clinical studies have addressed vascular, especially atherogenic, and metabolic effects of cannabinoid receptor stimulation, summarized in some comprehensive reviews [2,6–8]. Yet, little is known about a direct cardiac role and function of the ECS in health and disease. This review discusses current insights into the function of the classical cannabinoid receptors CB1 and 2 and the cannabinoid-sensitive target GPR55 in cardiac physiology and their potential therapeutic manipulation in the ischaemic heart.

2. Cannabinoid-sensitive receptors, G-protein coupling, cellular distribution and ligands

2.1. CB1

The ECS encompasses cannabinoid receptors, their endogenous ligands, namely the endocannabinoids (eCB), and the eCB synthesizing and degrading enzymes. The cannabinoid receptor 1 (CB1) was identified in 1990 and represents the most abundant G-protein coupled receptor (GPCR) in the central nervous system (CNS), but is also found in the peripheral, autonomous nervous system (ANS). Herein, CB1 is mainly expressed on and acting via pre-synaptic axon terminals of both, glutamatergic and gamma aminobutyric acid (GABA)-ergic neurons, inhibiting post-synaptic activation by preventing pre-synaptic neurotransmitter release [9,10]. Moreover, CB1 expression has been detected in the periphery, especially in various tissues involved in metabolism and energy expenditure, such as adipose tissue, liver, gastrointestinal tract, skeletal muscle and pancreas as well as in the reproductive system and on peripheral blood immune cells [11–13]. Some studies report its mRNA and protein abundance in adult rodent left ventricle (LV), in human LV tissue from healthy donors and in human atria [14–18] (Fig. 1). Regarding cardiac cell-type specific expression the literature states conflicting results. While Lepicier and colleagues observed CB1 to be localized almost exclusively on arterial and capillary endothelial cells in intact hearts, Currie et al. reported CB1 expression in isolated LV cardiomyocyte nuclei from adult male guinea pigs [19,20]. Here, the receptors are suggested to decrease inositol-1,4,5-triphosphate (IP3)-triggered calcium (Ca^{2+}) release, an event assumed to attenuate the pro-hypertrophic response upon pathological stimulation. The cardiomyocyte expression seems to be further affected by age, since neonatal rat ventricular cardiomyocytes could not be proven to express CB1 [16]. Yet, based on the current knowledge, the majority of CB1 effects on the cardiovascular system is suggested not to originate from cardiomyocyte signalling, but rather from activation of the sympathetic nervous system and simultaneous inhibition of the parasympathetic ANS [21].

CB1 signals in an agonist-biased manner. $G_{\alpha i/o}$ coupling inhibits adenylyl cyclase and cyclic adenosine monophosphate (cAMP)/protein kinase A-induced phosphorylation of ion channel proteins and activates inwardly rectifying potassium currents and mitogen-activated protein kinases (MAPK). $G_{\alpha q}$ or $_{\alpha s}$ coupling, in contrast stimulates intracellular Ca^{2+} rise [22,23].

2.2. CB2

The cannabinoid receptor 2 (CB2) is most abundant on immune cells, and herein especially on platelets and B-lymphocytes in the spleen and other hematopoietic organs as well as on peripheral blood mononuclear cells [11,12,24]. In the cardiovascular system, CB2 is present in various cell types, such as (adult and neonatal) LV cardiomyocytes, LV fibroblasts, vascular smooth muscle cells (VSMCs) and endothelial cells of larger arteries [13–16,19,25–27]. Weis et al. have shown CB2 and CB1 mRNA as well as protein (detected via immunohistochemistry) to be expressed at comparable levels in human LV tissue from donors without heart failure diagnostics [17]. Concurring with CB1, CB2 also couples predominantly to $G_{\alpha i/o}$, resulting in adenylyl cyclase inhibition and $_{\beta\gamma}$-subunit mediated activation of the MAPKs extracellular regulated kinase (ERK1/2), p38 and janus-kinase (JNK) [28]. However, some recombinant cell systems suggest CB2 to be also capable to signal via $G_{\alpha q}$ and thereby mediating a transient rise in extracellular Ca^{2+} mobilization in various cell lines [29,30].

2.3. GPR55

Endo- and phyto-cannabinoids have been demonstrated to not only stimulate the classical cannabinoid receptors CB1 and CB2, but also transient receptor potential channels and peroxisome proliferator activated receptors. The so far described cardiovascular actions of those GPCRs following eCB exposure are reviewed elsewhere [31]. Amongst the orphan GPCRs GPR18, 119 and 55, reported to be sensitive to cannabinoid stimulation, to date, only GPR55 is suggested to be involved in cardiovascular homeostasis and disease [32,33]. GPR55 was first identified in 1990 as the receptor for the endogenous lipid mediator lysophosphatidylinositol (LPI). By now, acylethanolamides, such as oleoylethanolamide (OEA) and palmitoylethanolamide (PEA) were shown to stimulate GPR55 [34]. Its affinity for phyto- and endocannabinoids was discovered only a decade ago [35–37]. However, given the low sequence homology of only 13.4% and 14.4%, it shares with CB1 and CB2, respectively, and the lack of the classical cannabinoid binding pocket, it failed to be classified as a classical cannabinoid receptor [38]. Therefore, GPR55 is rather referred to as a cannabinoid-sensitive or putative cannabinoid receptor. The rhodopsin-like receptor is expressed in the brain stem, frontal cortex, striatum, hypothalamus, cerebellum and hippocampus, but also in peripheral organs such as spleen, jejunum, ileum, adrenals as well as in skeletal muscle, bones, the vasculature and on immune cells [39]. So far, its low-level mRNA expression has been detected in the rodent LV and herein, in neonatal cardiomyocytes whereas validation of protein abundance in adult cardiac myocytes is debatable [32,33]. In contrast to CB1 and CB2, mainly coupling to $G_{ai/o}$, GPR55 has been reported to act via $G_{\alpha12,13}$ and $_{q/11}$, apparently depending on the ligand binding [40]. Meanwhile, GPR55-$G_{\alpha13}$ emerges as the predominant G-protein coupling. This leads to RhoA/ROCK activation, subsequent phospholipase C triggered IP3 generation, ultimately resulting in Ca^{2+} release from intracellular stores, ERK1/2 phosphorylation and activation of the transcription factors nuclear factor of activated T-cells and 'kappa-light-chain-enhancer' of activated B-cells, implying a role for GPR55 in contractile and immune responses [39].

2.4. Endocannabinoids

The first identified eCB N-arachidonoylethanolamine (anandamide,

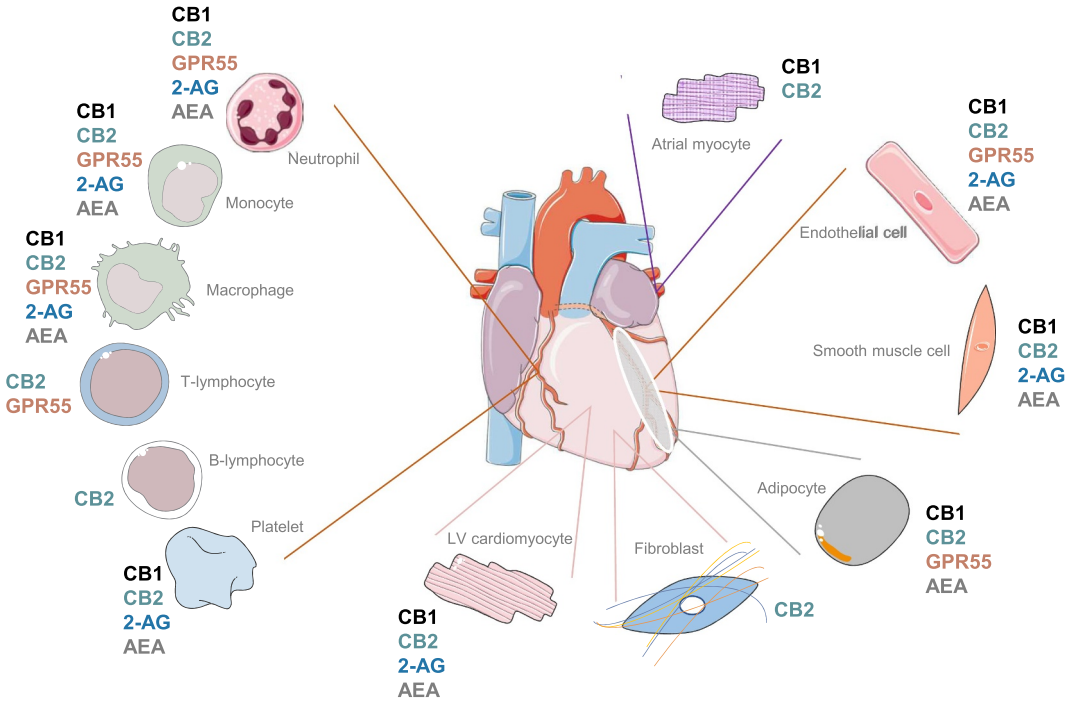

Fig. 1. Current cell-type specific mapping of cannabinoid-sensitive receptors and eCBs in the heart.
Overview about cell-type specific expression of CB1, CB2 and GPR55 in the heart and abundance of eCBs in cardiac cells where disease-triggered modulation of their synthesis has been described.

AEA) is found in various brain regions, in the liver, kidney, spleen, lungs and testis, but also in the circulation and the heart [41]. Within the latter it is generated by cardiomyocytes, endothelial cells, VSMCs and leukocytes, such as neutrophils, monocytes, macrophages and by platelets [42]. AEA is mainly synthesized via hydrolysis of N-acyl-phosphatidylethanolamine (NAPE) via NAPE phospholipase D but can also be generated from free arachidonic acid and ethanolamine by anandamide amidohydrolase/fatty acid amide hydrolase (FAAH) operating in reverse. AEA breakdown is mediated by FAAH to arachidonic acid and ethanolamine [41,43,44].

2-Arachidonoylglycerol (2-AG), the second most-well studied eCB is the most abundant eCB in the CNS. Besides, it has been detected in several peripheral tissues, such as the liver, kidney, spleen, and lungs, but also in the heart, secreted by endothelial cells and in the circulation in macrophages and platelets [41]. 2-AG is generated via hydrolysis of its lipid precursor diacylglycerol (DAG), mediated by DAG lipase (DAGL) [44]. Its degradation is catalysed by the hydrolytic monoacylglycerol lipase (MAGL) [45]. The eCBs AEA and 2-AG, both are generated on demand, in response to $G_{\alpha q/11}$ signalling mediated increase in intracellular Ca^{2+} concentrations. Immediately after their production, eCBs are secreted from the synthesizing cell in order to stimulate their receptors in an autocrine and paracrine rather than a systemic manner due to their hydrophobic nature. 2-AG is a partial CB1/CB2 agonist with similar affinity for CB1 and CB2, but higher stimulatory activity on CB2 while AEA is a partial CB1, CB2 and GPR55 agonist predominantly acting via CB1 [46]. However, G-protein activation studies have shown that 2-AG stimulates CB1-G-protein signalling efficiently while AEA represents only a weak CB1 partial agonist [28]. Moreover, it should be considered that acute effects of eCBs most likely differ from those provoked by chronic eCB exposure, especially since chronic elevations of 2-AG lead to CB1 desensitization [47]. The endogenous levels of AEA and 2-AG are not only the net result of the expression pattern and activity status of their generating and degrading enzymes and the endogenous availability of their precursors, but are also influenced by the nutritional regimen, and herein by the intake of eCB lipid precursors [48,49]. Altered tissue and plasma levels of AEA and 2-AG under different physiological and pathological conditions hint toward the potential role of the ECS in health and disease. Plus, the two eCBs are not equally regulated under a given pathological condition, suggesting that AEA and 2-AG elicit divergent roles [44].

3. Physiological actions of the ECS in the heart

While effects on appetite, pain perception and motor activity have been recorded for centuries, transient tachycardic and hypertensive responses triggered by marijuana consumption were first described in the 1970s and further elucidated in the 1990s [31,50]. Yet, not only exogenous stimulation by plant-derived cannabinoids, but also eCB signalling may exert various effects on the cardiovascular system, most presumably contributing to physiological homeostasis. The on demand-synthesis combined with the rapid metabolism of eCBs to arachidonic acid (metabolites) impedes the examination of their physiological cardiovascular actions. Currently, conclusions about ECS functions in cardiac homeostasis are merely drawn from characterization of cannabinoid-receptor KO mice and from actions of exogenous cannabinoids in the absence of cardiac stress (i.e. acute cardiac injury or sustained hyper/hypotensive scenarios). These respective approaches provide evidence that haemodynamic functions of the ECS are primarily linked to CB1 activity [51,52]. Under physiological conditions, CB1 stimulation exerts negative chronotropic, negative inotropic and vasodilatory responses in wild-type mice, whereas CB1 knock-out (KO) mice lack cannabinoid-inducible bradycardia and hypotension [53]. These cardiovascular effects originate either from cannabinoids binding to central receptors, thereby regulating neurotransmitter release, or from cannabinoids locally activating peripheral receptors on VSMCs, cardiomyocytes and endothelial cells or a combination thereof.

CB1 is expressed on sympathetic nerve endings innervating resistance vessels and the heart, where the receptor inhibits pre-synaptic noradrenaline release from post-ganglionic sympathetic neurons, thereby reducing post-synaptic adrenoceptor activation and subsequently diminishing catecholamine induced constriction and tachycardia. These neurohumoral responses are sensitive to CB1 blockade by

rimonabant (SR141617) [54,55]. Furthermore, synthetic cannabinoids inhibit adrenaline release from rabbit isolated adrenal glands, presumably via inhibition of acetylcholine release from pre-ganglionic sympathetic neurons, which can also be blunted by rimonabant [50]. Those insights suggest, physiological CB1-mediated effects on heart rate and blood pressure to be rather the consequence of its actions in the CNS than due to direct local effects on endothelial cells or cardiomyocytes [56]. This hypothesis is challenged by several studies demonstrating cannabinoid-mediated negative inotropy in the absence of central or peripheral sympathetic innervation in isolated rodent hearts and human atria, presumably involving CB1 signalling [18,57]. Moreover, intravenous single bolus AEA injections trigger a tri-phasic blood pressure response and bradycardia, with the third phase - only detectable in spontaneously hypertensive, but not normotensive rats - involving vascular and myocardial CB1 receptors [51,58]. Some of the above described findings emerge from studies validating the AEA-CB1 signalling by rimonabant-sensitive and SR144528 (CB2 antagonist)-insensitive responses. However, the presence of AEA-triggered vasodilation in the absence of functional CB1 receptors indicated the existence of a further AEA- and rimonabant-responsive endothelial receptor [59]. Waldeck et al. demonstrated GPR55 to be involved in AEA-induced Ca^{2+} signalling in endothelial cells and that CB1 and GPR55 mediate the endothelial AEA effects via distinct, interfering signalling pathways, depending on the status of integrin configuration [60]. So far, only in vitro assays demonstrated GPR55 to be responsive to AEA, as well as to other vasoactive cannabinoids, such as O-1602 and abnormal cannabidiol (abn-CBD), suggesting a role for the receptor in haemodynamic homeostasis and/or adaptations [60–62]. This hypothesis however requires in vivo validation. A further discrimination between GPR55- and CB1-mediated endothelial effects as well as between central and endothelial CB1 actions could probably be achieved by characterization of endothelial-specific CB1 and GPR55 KO animals.

A correlation between intracellular Ca^{2+} mobilization and GPR55 stimulation with cannabinoids or LPI could not only be verified in endothelial, dorsal root ganglia, carcinoma, and HEK cells, but also in cardiomyocytes [63,64]. The respective study claims that GPR55 initiates slow increase in intracellular Ca^{2+} via L-type Ca^{2+} channel entry and IP3-dependent Ca^{2+} release, with the latter potentiated by calcium-induced calcium release (CICR) through the ryanodine receptor [32]. This cellular response is triggered when GPR55 is localized in the sarcolemma of isolated neonatal myocytes. GPR55 localization in intracellular membranes, in contrast, was observed to trigger a fast and transitory Ca^{2+} release from acidic-like stores via the endolysosomal nicotinic acid adenine dinucleotide phosphate-sensitive two-pore channels. This is again further amplified by CICR, culminating in membrane hyper-polarization. These data hint toward a role of GPR55 in regulating cardiomyocyte and consequently cardiac contractility. An assumption further supported by a functional characterization of naïve, global GPR55 KO mice, showing that the receptor deficiency impairs β-adrenoceptor responsiveness age-independently and evokes systolic dysfunction age-dependently [33].

Not only ventricular inotropy, but also atrial contractility decreases upon CB1 activation in humans and rats as demonstrated by ex vivo approaches [18,65]. In isolated atria, this contractile decline was observed to be accompanied by decreased cAMP levels and increased generation of nitric oxide (NO) and cyclic guanosine monophosphate. Compared to CB1, haemodynamic and contractile effects of CB2 are less evident. So far, it has been reported that, in contrast to CB1, CB2 stimulation by AEA exerts cAMP-dependent positive inotropic effects in isolated rat atria [65]. Additionally, Currie and colleagues have detected CB1 and in isolated (cell-type-unspecific) cardiac nuclei and observed a reduced IP3R-mediated nuclear Ca^{2+} release upon AEA stimulation [20].

Given that CB1 and CB2 global KO mice do rather not exhibit strong (pathological) phenotypes under naïve conditions, one can assume the ECS to mainly play an important role in pathological situations [25,66]. Especially since, clinical data, as well as basic research point toward pronounced alterations in tissue- and cell-specific eCB signalling and altered cannabinoid receptor expression following tissue injury or pro-inflammatory stimulation [44].

4. Cannabinoids and their receptors in ischaemic heart disease

4.1. Impact of AMI on ECS components

Cardiac responses to acute ischaemia encompass maladaptive processes, such as inflammation, interstitial fibrosis, hypertrophy and ventricular dysfunction culminating in heart failure. The ECS is subjected to alterations following AMI, implying it to be an endogenous system involved in responses to the ischaemic insult. Patients with AMI exhibit increased CB1 and CB2 expression and elevated levels of AEA and 2-AG in the area at risk. This was shown to be accompanied by increased serum eCB concentrations and higher reactive oxygen species (ROS) and tumor necrosis factor-alpha (TNFα) levels in both, infarct-site coronary artery and radial artery [15,67].

Most animal models, used for investigating AMI related processes, isolate the ischaemic event from the initial MI-triggering coronary artery atherosclerosis. In contrast, data acquired from humans originate from AMI upon the preceding vascular inflammation and plaque formation. Therefore, the described up-regulation of pro-inflammatory factors in the LV arteries accompanying eCB generation might rather originate from atherosclerosis than the LV ischaemia per se. However, concurring with clinical data, in rodent MI studies, circulating and cardiac 2-AG levels increase during both, ischaemia/reperfusion (I/R) and permanent coronary occlusion [27,42,68]. This results from an increased expression of the 2-AG synthesizing enzyme and a concurrently decreased expression of the degrading lipase in the heart [68]. In contrast to 2-AG, elevated AEA levels could not be observed in all studies 24 h post permanent coronary occlusion [15,68]. Increased 2-AG and AEA levels in in vivo approaches correlate with stronger LV ROS and TNFα production and LV and cardiomyocyte-specific up-regulation of CB1 and CB2 [15,69,70]. A further elevation of 2-AG levels provoked by MAGL inhibition was shown to potentiate acute neutrophil and monocyte infiltration during acute inflammation and to aggravate infarction expansion and LV dysfunction during tissue remodelling after MI [68]. These tissue-damaging effects appear to be organ-specific, since MAGL inhibition prevents generation of oxidative stress and associated inflammation following I/R injury in the murine liver [71]. Inflammatory cytokines such as TNFα, IL-1β and − 6 have been described capable to directly trigger CB1 and CB2 up-regulation in human whole blood and peripheral blood mononuclear cells [12]. After 12 weeks permanent ligation of the left anterior descending coronary artery, no increase in CB1 expression could be detected in rat hearts [14]. Similarly, in LV tissue from end-stage heart failure patients (dilated cardiomyopathy), Weis et al. observed a drastic CB2 up-regulation and a concurrent down-regulation of CB1 mRNA and protein expression compared to biopsies from healthy controls [17]. It should be considered though that at heart failure stage, one may miss changes in CB1 expression as documented to occur in early phases post MI which then pave the way for consequent remodelling processes. Therefore, cause-effect relationships involving a CB1 regulation may be over-seen at later time-points. It is also conceivable that CB1 receptors are desensitized following chronic eCB elevations. In contrast, cardiac CB2 is up-regulated in acute as well as late phases of myocardial pathologies.

4.2. Impact of cannabis on AMI incidence

Cannabis smoking causes an acute, mostly well-tolerated short-term tachycardia, and long-term bradycardia and hypotension upon sustained consumption [21]. Yet, it has not been commonly ranked as a risk factor for acute coronary syndrome. However, while meta-analyses and retrospective studies do not correlate cardiac complications with

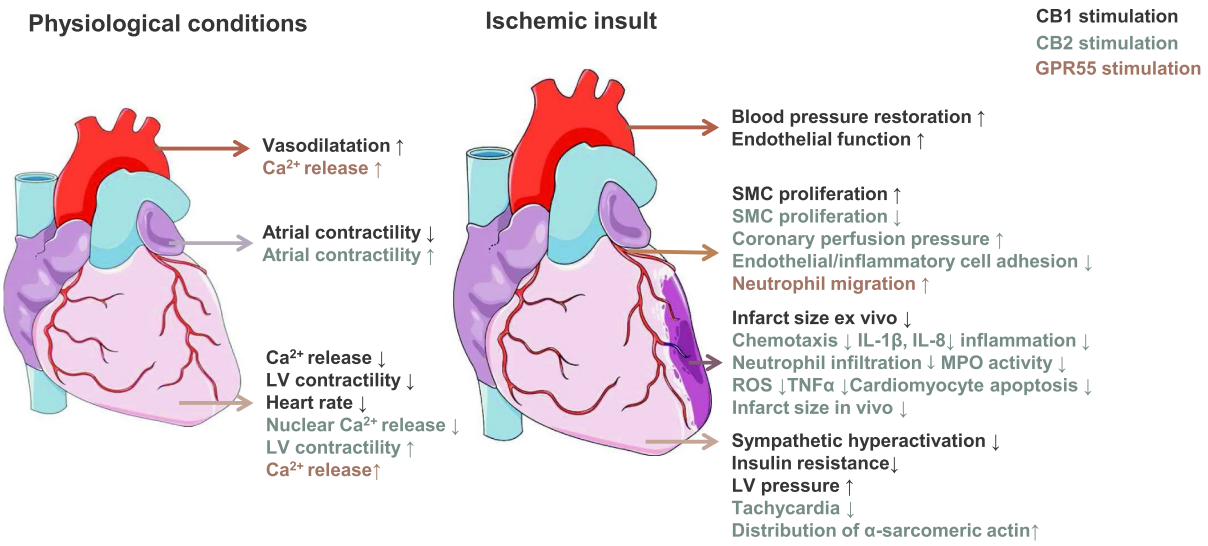

Fig. 2. Cardiac impact of cannabinoid receptors elucidated by receptor stimulation approaches.
Summary of cardiac effects mediated by CB1, CB2 and GPR55 stimulation in vitro, ex vivo and in vivo. CB1 = cannabinoid receptor 1; CB2 = cannabinoid receptor 2; LV = left ventricular; MPO = myeloperoxidase; SMC = smooth muscle cell.

prior cannabis consumption, individual case reports associate AMI incidence with temporally linked cannabis smoking [4]. Clinical reports describe the occlusion of a coronary artery in young, otherwise healthy, regular cannabis smokers with the cardiovascular event emerging during exercise training, either as a result of a plaque rupture or even without any evidence of atherosclerosis [72–74]. Furthermore, the recurrence of ischaemia triggered by a re-onset of marijuana consumption has been observed [75]. AMI in cannabis consumers may also be associated with higher short-term mortality. Yet, it should be considered that in regular marijuana smokers, AMI might not be fully and timely perceived due to analgesic, psychoactive and probably familiar cardiodepressant effects of the drug. Therefore, hospitalization and thrombolysis or stenting might just not happen in time to prevent the ultimate coronary occlusion. However, not only acute (ST segment elevation) MI, but also life-threatening arrhythmias have been reported as consequence of marijuana consumption. Two such patients presented with asystole and diffuse coronary vasospasm after acute cannabis abuse while others had suffered from ventricular or paroxysmal atrial fibrillation [76–79]. In most cases, drug tests were carried out and toxicological screening showed no drug abuse other than cannabis [76]. Yet, it is not fully approved that only plant cannabinoids and the subsequent stimulation of cannabinoid-sensitive receptors could be responsible for the ischaemic and arrhythmic events reported, since a myriad of variables has to be taken into account: frequency, dose and administration route regarding cannabis consumption, incomplete health records, existing (cardiovascular drug) treatments, concurrent abuse of tobacco, alcohol and other drugs, such as cocaine or synthetic cannabinoids (not traceable in urine samples), and disproportionate rates of comorbidities. Moreover, it should be considered that acute effects of (irregular) cannabinoid administration differ from those provoked by chronic cannabis exposure. It is well-known, that chronic elevations of the endogenous ligand 2-AG lead to CB1 desensitization [47]. Consequently, frequent cannabis consumption is most likely associated with sustained alterations in expression and sensitivity of the responsive receptors CB1, CB2, GPR55, transient receptor potential channels and peroxisome proliferator activated receptors. Further, plant cannabinoids may compete with eCBs regarding receptor binding and stimulation. So far, there is no information available regarding alterations in eCB levels in regular cannabis consumers or receptor expression pattern, for example determined in donor hearts. Therefore, to date, it is fully unknown in how far some of the reported supposedly marijuana-mediated adverse cardiovascular effects may originate from impeding the physiological and cardio-protective properties of the ECS. Yet, it should also be taken into account that the link between cannabis consumption and cardiac complications concluded in the above discussed case reports is challenged by cohort and cross-over studies. These studies revealed that even though marijuana is the most widely consumed drug worldwide, it only has a population attributable fraction (proportion of incidents, herein AMI, in the population that are attributable to the risk factor) of 0.8% as a trigger for AMI, with this increased risk additionally limited to the first 2 h after consumption [5,74,80,81]. The aetiology of cardiovascular complications described in the above discussed individual cases remains to be elucidated.

4.3. Impact of experimental ECS interventions on AMI outcome following permanent coronary occlusion

Acute and chronic myocardial ischaemia models allude toward a crucial impact of CB1 on the progressive LV remodelling process triggered by the ischaemic insult. CB1 antagonism has been reported to improve overall survival and to restrict infarct size in rodents. CB1 blockade by rimonabant treatment, initialized 7 days before MI and continued for 6 weeks post MI, lowered serum levels of the heart failure biomarker brain-natriuretic peptide, protected against functional deterioration and arrhythmia and mitigated LV fibrosis by reducing transforming growth factor β (TGFβ), hydroxyproline and collagen production [70]. Another study states that rimonabant administration initiated 7 days before experimental I/R reduces infarct size only in high fat diet fed, but not lean mice [82]. This was paralleled by a 21% decrease in body weight in the high fat diet group which one might assume a tremendous metabolic load, and which might raise the question if the observed beneficial effects might be at least partly due to metabolic and haemodynamic changes rather than due to direct cardiac effects.

Objecting the beneficial effects of CB1 antagonism, Wagner and colleagues observed CB1 antagonism by AM251 to rather aggravate features of adverse remodelling, such as LV dilatation and reduced LV systolic performance. This study claims, that chronic CB1 stimulation with the synthetic cannabinoid HU210 even restored blood pressure and endothelial function, prevented the decline in LV systolic pressure and increased LV diastolic pressure following coronary ligation in rats, but mainly in those with rather smaller infarctions [14] (Fig. 2). It should be considered carefully that HU210 represents not only a full agonist for CB1 and CB2, but also a GPR55 agonist even though it exerts a higher affinity for CB1 (Fig. 3). Beyond that, the CB1 antagonists

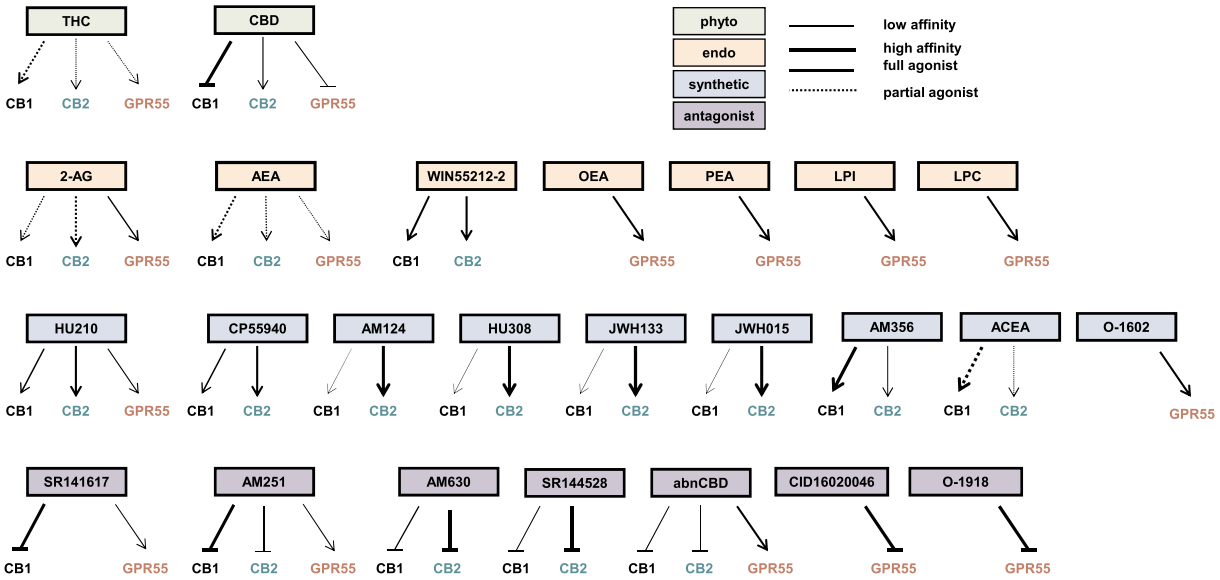

Fig. 3. Most well-studied phyto-, endo- and synthetic cannabinoid-sensitive receptor agonists and antagonists.
Schematic comparison of plant-derived, endogenous and synthetic agonists and antagonists regarding their binding affinity and efficacy to CB1, CB2 and GPR55. Endo = endogenous; phyto = plant-derived; CB1 = cannabinoid receptor 1; CB2 = cannabinoid receptor 2; THC = tetrahydrocannabinol, CBD = cannabidiol; 2-AG = 2-arachydonoylglycerol; AEA = anandamide; OEA = oleoylethanolamide; PEA = palmitoylethanolamide; LPI = lysophosphatidylinositol; LPC = lysophosphatidylcholine; ACEA = arachidonyl-2-chloroethylamide; SR141617 = Rimonabant; abnCBD = abnormal cannabidiol.

AM251 and rimonabant also bind GPR55 and could hereby exert stimulatory effects on the latter, as shown in HEK cells [40,83,84]. The distinct role of CB1 in post MI wound healing requires further confirmation via highly selective stimulation and/or blockade and by receptor KO studies. So far, CB1 KO has been shown to mitigate LV inflammation, oxidative stress, apoptosis and fibrosis as well as dysfunction in a mouse model of diabetic cardiomyopathy [66]. In contrast, Liao et al. report CB1 KO to aggravate pressure-overload induced excessive catecholamine release and loss of lusitropy [85,86].

However, a beneficial impact of ECS activation on post MI outcome is further underpinned by a study showing that administration of an ultra-low THC dose (2 μg/kg) prior to experimental MI reduced infarct size, cardiac troponin I level, systolic dilatation and mitigated functional decline, assessed 24 h following MI induction [87].

Since THC represents a partial agonist for CB1, CB2 and GPR55, the cannabinoid receptor mediating these cardio-protective effects remains to be determined. Yet, an in vitro study in hypoxic neonatal murine cardiomyocytes identifies CB2 as the receptor responsible for THC-mediated protection by preventing the leakage of lactate dehydrogenase (LDH) and maintaining the morphological distribution of α-sarcomeric actin [16].

In vivo, in AMI and I/R approaches, infarct size reduction as well as decreased ROS and TNFα levels could be achieved by targeted, selective CB2 stimulation with its synthetic, highly potent agonist HU308 and blocked by its inverse agonist AM630 [15]. A crucial role for CB2 in the ischaemic heart is further emphasized by characterization of CB2 KO animals. In isolated murine embryonic cardiomyocytes and M1 and M2 macrophages, hypoxia as well as inflammatory stimulation has been reported to increase cellular CB2 expression. This up-regulation is assumed to be beneficial since induction of hypoxia in CB2 KO cardiomyocytes resulted in a higher rate of apoptosis, myofibroblast activation and increased migration of pro-inflammatory M1 macrophages toward the apoptotic cells [25,69]. Horckmans et al. confirmed the cardio-protective potential of CB2 in a KO study in vivo. The researchers observed more pronounced MI-triggered LV fibrosis and aggravated reduction in ejection fraction in $CB2^{-/-}$ mice and highlighted a role for lymphoid clusters within the pericardial adipose tissue in the unfavourable effects of CB2 deficiency [88]. CB2 deficiency has further been linked to amplified, MI-triggered neutrophil release from the bone marrow into the circulation [68]. Bone marrow hematopoietic stem and progenitor mobilization as well as release of mature leukocytes crucially determine acute induction and subsequent resolution of inflammation at the infarct site [89]. Balenga et al. suggest a CB2-GPR55 cross-talk in neutrophils to be essential for their migration to the site of injury [90]. Apart from the hypothesis that some effects attributed to supposedly selective ligands for CB1 or CB2 are additionally linked to GPR55 signalling, hitherto, the literature lacks any insights into a potential role of GPR55 in ischaemic heart disease.

4.4. Impact of experimental ECS interventions on AMI outcome following ischaemia reperfusion

4.4.1. Infarct size, acute LV inflammation and fibrosis

If blood flow is blocked by thrombotic occlusion due to atherosclerotic plaque rupture or if coronary artery stenosis exceeds 80%, the myocardium down-stream becomes ischaemic. This results in irreversible tissue damage when insufficient blood and oxygen supply persists longer than 20–40 min. A timely reperfusion of the affected heart by re-opening the occluded artery limits infarct size, but simultaneously provokes further damage to the heart. This so called I/R injury encompasses reactive oxygen and nitrogen species (RNS) and inflammation at the site of injury which in turns amplifies again ROS and RNS production [6].

The potential of the ECS and herein in particular CB2 to impact on I/R outcome has been demonstrated by various ex vivo and in vivo studies. In isolated hearts, perfusion with the endogenous lipid mediators, 2-AG and PEA, but not the eCB AEA prior to and continued during ischaemia, decreased LDH and creatine kinase, reduced infarct size and improved myocardial recovery. This cardio-protection involved p38, ERK1/2, as well as PKC activation and was blunted upon CB2 blockade by SR144528. Yet, the CB1 antagonist rimonabant could also partially inhibit the beneficial effects of 2-AG [91]. Targeted CB1 activation by ACEA reduced infract size as efficaciously as CB2 stimulation with JWH015. This CB1-, but not the CB2-mediated effect, was NO-dependent and supports a role for CB1 in the endothelium of injured hearts rather than ~~i~~n cardiomyocytes, as shown for CB2 [19]. Objecting these results, a heat stress preconditioning approach in isolated rat hearts demonstrated that infarct-size reduction was not altered

by rimonabant perfusion, but abolished by both, SR144528 and L-NAME. This indicates a NO-dependent cardio-protection mediated by CB2 activation [92]. Another study reports that limitation of the infarction area in isolated rat hearts can be achieved not only by 2-AG, but also by AEA. This favourable impact could be blocked by either CB1 or CB2 antagonism with rimonabant or SR144528, but neither mimicked by the non-selective full agonist HU210 nor by selective CB1 (AM356 or ACPA) or CB2 (JWH133) stimulation per se or by a combination of the latter [93]. These findings suggest a further cannabinoid-sensitive receptor to be involved in mediation of beneficial effects of at least some cannabinoid-receptor ligands. While antagonizing CB1, rimonabant has also been debated to act on GPR55, either as an antagonist or as an agonist [40,63,83]. Therefore, cardiac effects upon its administration might at least partly involve GPR55-mediated downstream signalling. Additionally, PEA, a lipid mediator not binding to CB1 or CB2, but showing high affinity for GPR55 and PPAR, decreased the levels/activity of LDH and creatine kinase, reduced infarct size and improved myocardial recovery to a comparable extent as 2-AG ex vivo [91]. Future studies, applying synthetic cannabinoids or endogenous lipid mediators, should clearly discriminate between the different receptor targets to identify the GPCR responsible for the respective I/R outcome.

Ex vivo studies rule out the impact of circulating cells, recruited to the injured heart, whereas in in vivo studies ECS effects involve not only immune cell infiltration and signalling, but also CNS-triggered responses. Contradicting the ex vivo findings that JWH133 fails to promote protection from I/R injury, in vivo rat and mouse studies revealed that JWH133 administered either prior to ischaemia on-set or before reperfusion reduced infarct size by triggering the pro-survival phosphatidyl-inositol-3 kinase/protein kinase B and ERK1/2/STAT-3 cascades, thereby attenuating cardiomyocyte apoptosis and ROS generation. This benefit is probably due to the observed reduction in acute neutrophil infiltration at the site of injury which in turn might be attributed to JWH133 inhibition of TNFα induced chemotaxis and integrin CD18/CD11b up-regulation as observed in human neutrophils [25,94,95]. A key role for neutrophils in CB2 promoted cardio-protection is further supported by decreased myeloperoxidase activity and reduced levels of the neutrophil-attracting cytokines IL-1β and -8 in the ischaemic myocardium upon WIN55212-2 triggered CB2 activation [96]. Cytokine production and neutrophil infiltration following endothelial adhesion represent the first inflammatory response of the myocardium after an ischaemic insult. Beneficial effects attributed to ECS modulation are mainly the result of its impact on acute inflammation and wound healing, paving the way for reparative mechanisms, and subsequently improving overall outcome post MI.

The above discussed data clearly demonstrate a protective impact of CB2 stimulation herein, while CB2 deficiency exacerbates I/R injury and impairs wound healing following MI. One day post I/R, wild-type hearts exhibit smaller infarcts than CB2−/− hearts and even smaller infarcts when injected with JWH133 at reperfusion. Cardiac deterioration in CB2−/− mice is associated with enhanced apoptosis at day 3, increased macrophage infiltration in the infarct area and the adjacent remote septum, transmural scar formation at day 7 and exaggerated fibrosis and LV dysfunction at 28 days after the ischaemic insult [25,97]. A mouse model of repetitive, brief I/R periods (below MI-induction extent), mimicking hibernating human myocardium, confirmed CB2 deficient mice to exhibit more apoptosis and irreversible dysfunction 2 months after ischaemia. In contrast, wild-types showed an increase in CB2 expression in ischaemic cardiomyocytes and a transient increase in plasma AEA levels and no signs of cardiac deterioration [27]. The unfavourable outcome of CB2 deficient mice was associated with the lack of the myosin heavy chain isoform switch, characteristic for hypertrophic, energy starved myocardium, with reduced anti-oxidative capacity and impaired signalling of CCL2, a chemokine demonstrated to be crucially involved in the pathology of ischaemic cardiomyopathy, and a prolonged inflammatory response due to a delayed activation of the pro-resolving M2a macrophage population [98]. A vital role for CB2 in macrophage function during ischaemia has also been demonstrated by showing that CB2 expressed on pro-inflammatory macrophages affects cardiomyocyte survival [69]. These findings indicate CB2 to crucially impact on the initial phase of ischaemic heart disease and therefore on subsequent repair processes which in turn influence the degree of residual function post MI.

Beneficial impact of the ECS on MI outcome clearly involve anti-inflammatory effects affecting subsequent tissue remodelling, and modulation of the sympathetic and parasympathetic activity, thereby influencing LV function.

4.4.2. LV function

Myocardial infarction leads to acute arrhythmia and hypotension and decreased adrenoceptor-responsiveness and overall LV dysfunction in the long-term. Disease models other than AMI indicate eCBs derived from macrophages and platelets to be involved in hypotension associated with different shock-scenarios as well as liver cirrhosis. Independent of the experimental model, rimonabant prevents or reverses the hypotensive state [99]. Concurring with this, AMI studies in the rat report circulating monocytes and platelets to generate AEA and 2-AG and that the decline in mean arterial pressure upon AMI could be prevented by rimonabant treatment prior to the coronary occlusion. Yet, the CB1 blockade increased MI-associated tachycardia and even early mortality [42]. However, the assignment of hypotensive effects to the CB1 receptor based on rimonabant studies remains debatable. Batkai and colleagues demonstrated lipopolysaccharide-induced hypotension to be sensitive to rimonabant in CB1 KO as well as CB2 KO mice [59]. Therefore, a putative MI-triggered vasoactive role for other cannabinoid-sensitive receptors such as GPR55 needs to be elucidated. Beyond that, not only hypotensive but also hypertensive conditions promote eCB release from platelets, monocytes and endothelial cells, resulting in elevated circulating levels thereof in humans and rodents [51]. Myeloid-specific cannabinoid receptor KO mice and/or studies investigating the impact of eCB degrading and synthesizing enzymes might add further insights.

An ischaemic preconditioning approach in isolated rat hearts indicates that I/R attenuates vasodilation afforded by endothelium-dependent serotonin, but not by endothelium-independent vasodilation. Preconditioning prevented this dysfunction in the ex vivo model and could be mimicked by 2-AG and PEA perfusion. An inverse CB2 agonist blocked the protective effect of both cannabinoids while CB1 blockade only affected PEA conditioning [100]. Depending on the prevailing haemodynamic imbalance, the eCBs might act via one or the other responsive receptor to counteract exaggerated vasodilation or vasoconstriction, respectively. In vitro, ex vivo and in vivo studies, focussing on hypertension in the absence of acute cardiac tissue injury, identified CB1 as the receptor counteracting angiotensinII-, catecholamine-, and trans-aortic constriction-induced vasoconstriction [70,85,101].

Regarding cardiac contractility, acute CB1 blockade by rimonabant elevated maximal and mildly reduced minimal peak rate of developed LV pressure (dP/dt_{max} vs. dP/dt_{min}) hinting toward improved inotropy in 6-weeks infarcted but not sham-operated or naive rat hearts [70,102]. Besides, chronic daily rimonabant injection, initiated before and continued for 6 weeks after MI, improved systolic and diastolic LV function, prevented excess arterial stiffness and normalised QRS complex pattern. Another rat study investigated a role of eCBs in the beneficial effect of remote ischaemic preconditioning (triggered by occlusion and reperfusion of the mesenteric artery) on cardiac I/R injury. The researchers revealed that AM630, but not AM251 administration prior to the remote conditioning protocol abolished the reduction in infarct size, in frequency and duration of premature ventricular contractions, in ventricular tachycardia and in fibrillation [103]. These protective effects are usually achieved by remote conditioning. An AM630 effect on I/R triggered hypotension however could not be observed. This suggests a role for CB2 in stabilizing sinus rhythm but not

endothelial function upon I/R. In diabetic rats however, CB2 activation could also improve I/R outcome by counteracting tachycardia, but additionally exerted haemodynamic effects by restoring coronary perfusion pressure [104].

Functional deterioration as well as remodelling of the heart following MI results not only from loss of contractile tissue in the infarcted area and subsequent inflammation but also from excessive catecholamine release and therefore sympathetic hyper-activation. CB1 activation is postulated to protect against sympathetic hyper-activation following MI via inhibition of excessive NE release from nerve fibres innervating the heart and vessels [102]. This is further supported by a study in rabbits, where unselective cannabinoid receptor agonists, administered into the medulla oblongata, increased plasma NE levels, renal sympathetic nerve activity and blood pressure and reduced heart rate. This could be attenuated by rimonabant [56]. Slavic et al. report that spontaneous hypertensive obese rats treated with rimonabant for 2 weeks showed improved ejection fraction and fractional shortening, yet, interestingly, the continuous CB1 antagonism did not affect chronotropy or blood pressure in this study [70]. Nevertheless, it has to be taken into account, that neither haemodynamic nor contractile effects can be exclusively linked to a single family of receptors. Cannabinoid receptors can interact and hetero-dimerize with various other GPCRs. In this context, an interaction between the ECS and adenosine-A1-receptor signalling has been observed in cannabidiol-mediated reduction in frequency and duration of arrhythmic events upon brief ischaemia and subsequent reperfusion in rats [105].

4.4.3. Cardiomyocyte metabolism

In response to tissue injury, the heart switches its substrate metabolism from the use of fatty acid toward uptake and use of glucose. I/R impairs this adaptive response and aggravates cardiac injury by promoting inflammation and lipotoxicity. Various studies hint toward a direct correlation between dysregulated glucose uptake and insulin resistance and cardiac dysfunction.

The CB1 antagonist rimonabant was initially thought of as a promising obesity therapy by improving glucose and lipid profiles and was thereby meant to reduce cardiovascular risk before being removed from the market due to deleterious psychological side-effects. The improved lipid metabolism in obese patients and mice fed with a high fat diet was achieved by reduction of plasma triglycerides, low-density lipoprotein cholesterol, leptin, insulin and glucose and concurrent raise in plasma high-density lipoprotein cholesterol and adiponectin level [106,107]. Adiponectin is also produced by cardiomyocytes [108]. Yet, its transcriptional up-regulation following CB1 blockade has so far only been confirmed in adipocytes [109,110]. Furthermore, Lim and colleagues could not detect any rimonabant induced alterations in serum adiponectin levels to be involved in the infarct size limiting effect of the CB1 antagonism [82].

Chronic lipid overload results in increased cardiac lipid uptake followed by insulin resistance. Insulin resistance again contributes to the development of cardiac dysfunction, culminating in diabetic cardiomyopathy. Regarding insulin sensitivity, CB1 blockade and deletion have been reported to prevent especially hepatic insulin resistance in mice [111]. A more recent study, performed in vitro in human embryonic stem cell derived and rat cardiomyocytes, demonstrated that 2-AG counteracts insulin resistance and impaired glucose uptake evoked by TNFα-triggered inflammation [112]. The proposed mechanism includes 2-AG-mediated CB1 and Ca^{2+}/calmodulin-dependent protein kinase β (CaMKKβ) signalling. This results in activation of AMP-activated protein kinase K (AMPK), an enzyme crucially involved in energy metabolism. AMPK has been shown to be stimulated in the hypothalamus and the heart and to be inhibited in liver and adipose tissue by THC and 2-AG [113]. These observations suggest 2-AG to be involved in metabolic homeostasis in cardiomyocytes, presumably by activating CB1.

GPR55 stimulates insulin secretion from pancreatic β cells upon LPI and LPC binding and concurrently decreases glucose levels [64]. More recently, it has been shown that GPR55 activation increases insulin signalling in myotubes in skeletal muscle [114]. In addition, the receptor has been discovered to contribute to the manifestation of obesity and diabetes [38]. This may hint toward at least an indirect effect on cardiac energy homeostasis, yet, its impact on metabolically imbalanced myocardium upon ischaemic injury remains elusive.

5. Perspectives

Experimental insights clearly demonstrate a potent impact of ECS interventions on extent and progression of ischaemic heart disease and the functional outcome thereafter. In brief, CB2 agonism attenuates the degree of MI-triggered inflammation, apoptosis and fibrosis at the site of injury and simultaneously preserves left ventricular function. CB1 antagonism has been reported to either mitigate inflammation, oxidative stress, infarction expansion and to improve cardiac performance or to even aggravate functional decline, negative lusitropy and left ventricular dilatation following MI, presumably depending on the (unspecific) antagonist administered in the respective studies. Moreover, GPR55 is suggested to be crucially involved in cardiomyocyte and consequently cardiac contractility and β-adrenoceptor responsiveness. Thus, targeted agonism/antagonism of cannabinoid-sensitive receptors represents a promising therapeutic strategy to mitigate detrimental adverse cardiac and vascular processes associated with MI. But, nevertheless, unselective ant/agonists well as tissue- and cell-specific receptor distribution, combined with the highly dynamic regulation of eCB generation in various cell-types, and the lack of specific CB1 and GPR55 antibodies complicate to date the assignment of observed effects to, and the selective stimulation/inhibition of a respective ECS member. Future studies should address these challenges. Moreover, a distinct role of the ECS in cardiomyocyte hypertrophy per se, as a crucial contributor to adaptive and maladaptive remodelling in various cardiac diseases, remains to be elucidated. In conclusion, further research is highly warranted to better understand and to eventually exploit the capacity of ECS modifications for the treatment of cardiac disorders.

Transparency document

The Transparency document associated with this article can be found, in online version.

Acknowledgements

This work was supported in part by the Deutsche Forschungsgemeinschaft (STE-1053/5-1 to Sabine Steffens) and the Friedrich-Baur funding of the Ludwig-Maximilians-Universität München (to SL. P.).

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